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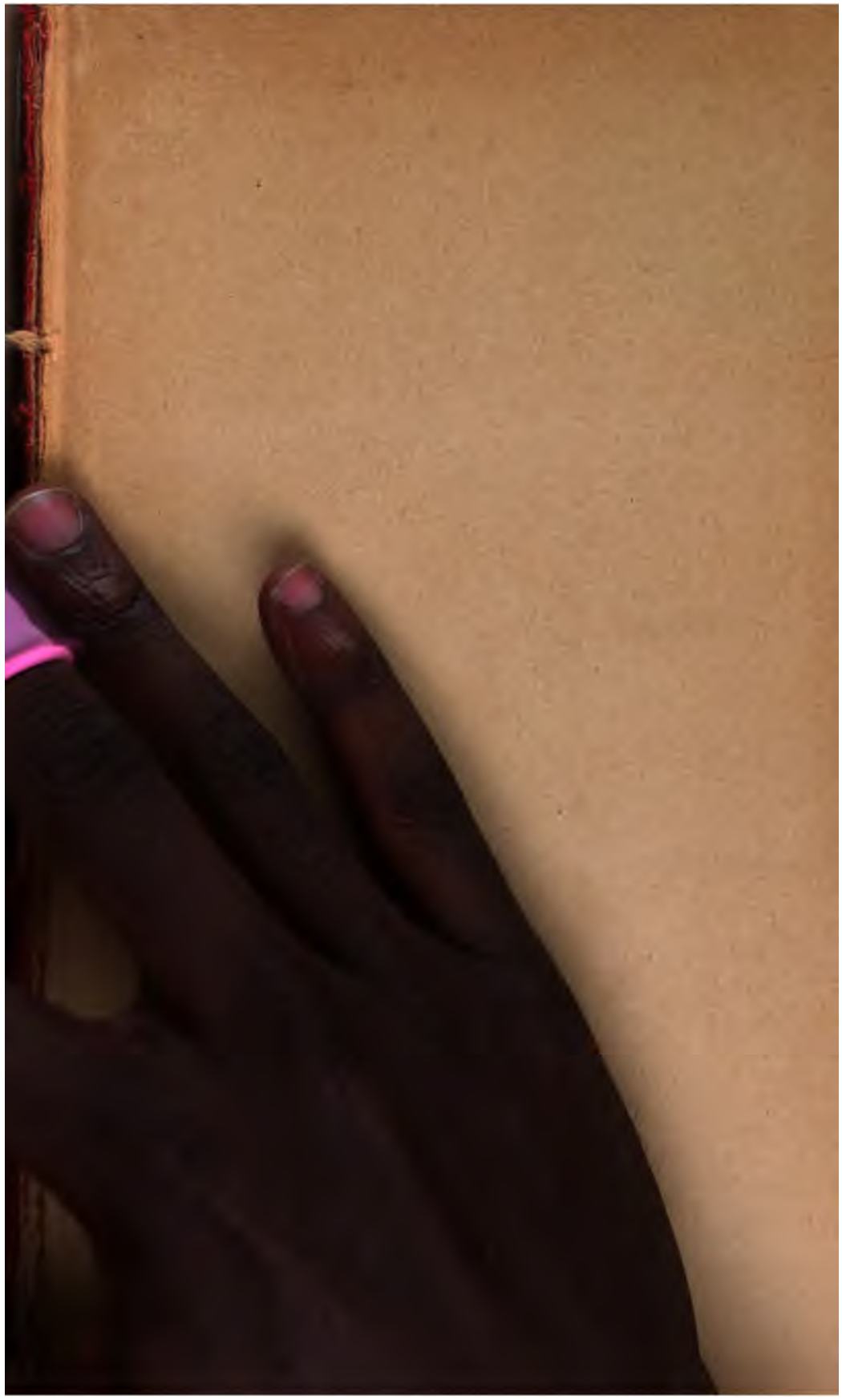

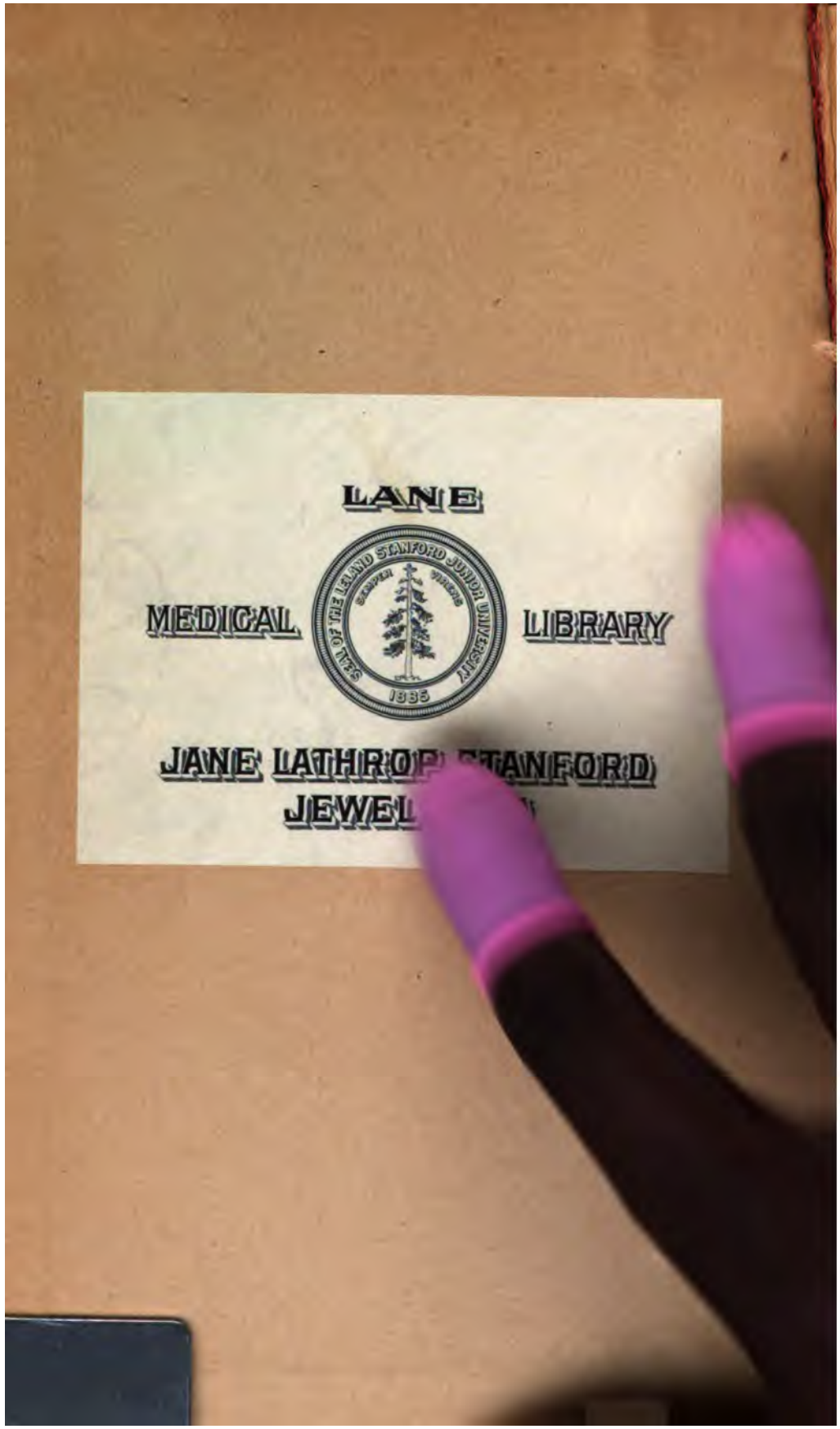
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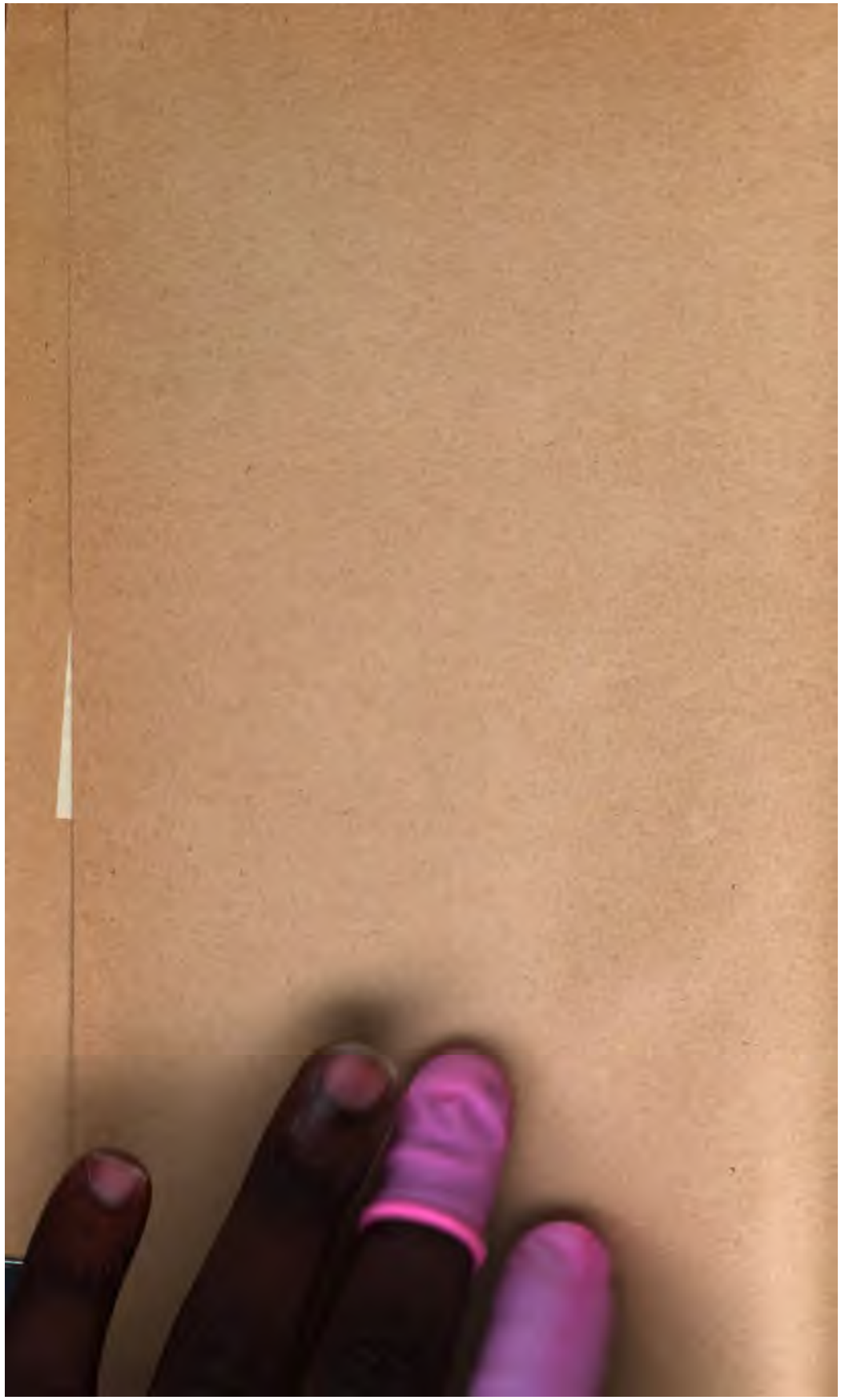

TRANSACTIONS

OF THE

Fifteenth International Congress on Hygiene and Demography

WASHINGTON

September 23-28, 1912

PUBLISHED BY THE COMMITTEE ON ORGANIZATION

EDITED BY THE SECRETARY GENERAL

VOLUME II

PART I—PROCEEDINGS OF SECTION I
Hygienic Microbiology and Parasitology

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[1] Prof. Philip Hanson Hiss, professor of bacteriology in the College of Physicians and Surgeons, New York, died February 27, 1913, in the forty-sixth year of his age.

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SECTION I.

HYGIENIC MICROBIOLOGY AND PARASITOLOGY.

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REPORT OF SECRETARY.

Prof. THEOBALD SMITH, *President Section I*,

Fifteenth International Congress on Hygiene and Demography.

SIR: In accordance with the provision of Article XII of the regulations of the congress, we herewith submit a report of the section proceedings of the meeting held at Washington, September 23 to 28, 1912, together with such manuscripts of the papers read as have been delivered into our hands as secretaries pro tempore, Dr. Philip Hanson Hiss being unavoidably absent.

MONDAY, SEPTEMBER 23—3 P. M.

The first session was called to order by the president, Prof. Theobald Smith, who announced the following honorary presidents of Section I:

Prof. FRIEDRICH LOEFFLER, of Greifswald, Germany; Prof. AUGUST GAERTNER, of Jena, Germany; Prof. GEORGE NUTTALL, of Cambridge, England; Prof. ADOLF DIEUDONNÉ, of Munich, Germany; Regierungsrat Dr. A. WEBER, of Berlin, Germany; Prof. ALFRED PETTERSSON, of Stockholm, Sweden; Prof. KARL LANDSTEINER, of Vienna, Austria.

Dr. D. L. Harris, nominated by Dr. V. C. Vaughan, was made temporary secretary.

Papers were presented in the symposium on filterable viruses as follows:

Some Experiments upon the Nature of the Virus of Rabies, by Drs. Daniel Warren Poor and Edna Steinhardt, Department of Health, New York City.

Natural and Induced Immunity to Typhus Fever, by Drs. Goldberger and Anderson, United States Public Health Service, Washington, D. C.

Observations on a Chicken Sarcoma and its Filterable Cause, Drs. Rous and Murphy.

TUESDAY, SEPTEMBER 24—9.30 A. M.

The second session was called to order by the president, Prof. Theobald Smith, who presided throughout the morning.

Papers were presented on the subject of special selective media for microorganisms, as follows:

Selective Culture Medía for Growth of Cholera Spirilla, by Prof. Dr. Adolf Dieudonné, University of Munich, Germany.

Egg Agar as Culture Medium for Cholera Spirilla, by Dr. Charles Krumwiede, jr., New York City.

A Plating Medium for the Recognition of Acid and Nonacid Producing Bacteria, by Dr. A. J. Bendick, College of Physicians and Surgeons, Columbia University, New York City.

Special Culture-media for Pure Cultures of Amebae found in Intestines of Animals, Dr. A. W. Williams, research laboratory, New York City.

Bacterial Water Examination, by Prof. Edwin O. Jordan, University of Chicago, Chicago, Ill.

Cultivation of Malarial Plasmodia in Vitro, by Dr. C. C. Bass, New Orleans, La. This subject was illustrated with lantern slides.

The following members of the congress joined in the discussion:

Dr. E. Libman (New York City), Dr. Karl Landsteiner (Austria), Capt. C. F. Craig, U. S. Army (Washington, D. C.), Prof. Dr. A. Gaertner (Jena, Germany), Dr. F. L. Rector (Brooklyn, N. Y.), Prof. Edwin O. Jordan (Chicago, Ill.), Dr. Wm. H. Park (New York City).

Tuesday, September 24—2.10 p. m.

The third session was called to order by the president, Prof. Theobald Smith, who presided throughout the afternoon.

Papers were presented upon miscellaneous subjects, as follows:

A Critical Study of Acid-fast Bacilli Cultivated from the Human Leprous Lesion, with Especial Reference to their Etiological Significance, by Prof. Charles W. Duval, Tulane University, New Orleans, La.

Influenza Meningitis, Experimental and Clinical, by Dr. Martha Wollstein, Rockefeller Institute for Medical Research, New York City, was read by title, its author being absent.

Preventive Inoculations: Experimental and Clinical Studies on the Use of Leukocytic Extract in the Treatment of Erysipelas, Pneumonia, et cetera, by Prof. Philip Hanson Hiss, jr., Columbia University, New York City. (Read by Dr. W. H. Park.)

The Production of Antirabic Immunity by Intraspinal Injections of Virus, by Dr. D. L. Harris, Bacteriologist to Hospital Department, St. Louis, Mo.

The Etiology of Trachoma, by Dr. Anna W. Williams, Research Laboratory, Department of Health, New York City.

The following members of the congress took part in the discussion: Dr. C. Wellman (New Orleans, La.), Dr. Libman (York City), Dr. Karl Landsteiner (Austria).

WEDNESDAY, SEPTEMBER 25—9.30 A. M.

The fourth session was called to order by the president, Prof. Theobald Smith.

Papers were presented upon the topic of paratyphoid and paratyphoidlike bacilli with especial reference to their dissemination in nature and their relation to man and animals as follows:

A Report of Work Done at the Kaiserlichen Gesundheitsamt, by Regierungsrat Prof. Dr. A. Weber, Berlin, Germany.

Studies on Typhoid and Paratyphoid Organisms at the Lister Institute. Dr. J. Henderson Smith, Lister Institute, London, England.

Paratyphoid and Allied Bacilli, including the Bacteriology of Animal Foods, by M. le Dr. Sacquepée, Prf. au Val-de Grâcé, Paris, France.

Representatives of the Gärtner Group Isolated from the Tissues of Laboratory Animals, by Dr. John C. Torrey, Cornell University Medical College, New York City.

A Bacteriological Examination of Market Milk, by Dr. P. G. Heineman, University of Chicago, was read by title, its author being absent.

The following members of the congress joined in the discussion: Dr. Wm. H. Park (New York City), Dr. W. Fornet (Berlin), Dr. E. Libman (New York City), Prof. C. E. A. Winslow (New York City), Dr. William H. Welch (Baltimore, Md.).

The recommendation for an international commission to prepare a standard of procedure for determining B. Coli, as suggested by Dr. Weber, was then considered by the section.

Prof. William H. Welch moved that a committee be established, with Dr. Weber as chairman, and that members be added as the commission desired. This motion, while not acted upon at this time, was assented to by the leading members of the section, and was forwarded to the Permanent International Commission.

The following additional papers were then read:

La Tuberculosis Experimental en las Grandes Alturas, by Dr. Nestor Morales.

Milzbrand und Salvarsan, Dr. Geo. Becker, Plauen, Germany.

THURSDAY, SEPTEMBER 26—9.15 A. M.

The section joined with Section V in a symposium on poliomyelitis, etiology, and mode of transmission.

Dr. Hermann M. Biggs, president of Section V, presided.

The following papers were presented:

Epidemic Poliomyelitis in Norway, by Prof. Dr. Francis Harbitz, Koneglige Frederiks Universitet, Christiania, Norway.

Sanitary Measures against Poliomyelitis, by Privat-Docent Dr. Karl Landsteiner, k. k. Universität, Vienna, Austria, and Dr. Simon Flexner, Rockefeller Institute for Medical Research, New York City.

The Etiology of Poliomyelitis and Prophylactic Measures, by M. Neustaedter, M. D., Ph. D., instructor in neurology, New York University and Bellevue Hospital Medical College, New York City.

Ueber die Verbreitungsweise der epidemischen Kinderlähmung und die Verhütung ihrer Verbreitung, by Prof. Alfred Pettersson, Stockholm, Sweden.

Die histologischen Veränderungen im Rückenmarke des Affen bei experimenteller Poliomyelitis, by Prof. Alfred Pettersson, Stockholm, Sweden.

Einige epidemiologische Beobachtungen bei der Kinderlähmungsepidemie in Schweden, 1911-1912. Kurzes Resumé, by Prof. Alfred Pettersson, Stockholm, Sweden.

Anterior Poliomyelitis, as observed in Massachusetts, 1907-1911, by Dr. Mark W. Richardson, Secretary State Board of Health, Boston, Mass.

A Preliminary Announcement of Observations on the Rôle of Stomoxys Calcitrans in the Spread of Anterior Poliomyelitis, by Prof. M. J. Rosenau, Harvard University, Boston, Mass.

The following members of the congress joined in the discussion:

Prof. Geo. Nuttall (Cambridge, England), Prof. Dr. Friedrich Loeffler (Germany), Dr. Karl Landsteiner (Vienna, Austria), Prof. A. Pettersson (Stockholm, Sweden), Prof. W. S. Thayer (Baltimore, Md.), Dr. Francis E. Fronczak (Buffalo, N. Y.), Dr. M. J. Rosenau (Boston, Mass.), Dr. Frankl-Hochwart (Vienna, Austria).

Thursday, September 26—2.15 p. m.

The fifth session was called to order by Prof. Charles W. Stiles. The following papers were read:

The Relation of Parasitic Amaebae to Disease, by Capt. Charles F. Craig, United States Army, Washington, D. C.

The Identification of the Pathogenic Entameba of Panama, by Dr. Samuel T. Darling, Ancon Hospital, Ancon, Canal Zone.

Nomenclature of Genera and Species of Amebae, by Howard Crawley, zoological division, Department of Agriculture, Washington, D. C.

Present Status of Knowledge of Structure of Nucleus of all Known Parasitic Amebae, by Dr. M. J. S. von Prowazek, Seemannskrankenhaus und Institut für Schiffs- und Tropenkrankheiten, Hamburg, Germany, was read by title, its author being absent.

Compendium of all Amebae, Arranged According to their Hosts, Regardless of the Zoological Status of the Species of Amebae, by Albert Hassall, assistant zoologist, United States Department of Agriculture, Washington, D. C.

Bibliography of Parasitic Amebae, by Albert Hassall, assistant zoologist, United States Department of Agriculture, Washington, D. C.

Present Status of Zoological Classification of the Parasitic Amebae (Genera and Species); also Present Status of Technique in Studying Amebae (Free and Parasitic), by Prof. Gary N. Calkins, New York City, were read by title, their author being absent.

The following members of the congress joined in the discussion: Dr. C. Wellman (New Orleans, La.), Dr. Charles F. Craig (Washington, D. C.), Dr. Samuel T. Darling (Ancon, Canal Zone).

FRIDAY, SEPTEMBER 27—9.30 A. M.

The sixth session was called to order by Prof. Theobald Smith.

Papers were presented in the symposium on anaphylaxis, as follows:

The Relation of Anaphylaxis to the Infectious Diseases, by Dr. Victor C. Vaughan, University of Michigan, Ann Arbor.

Studies on the Locus of Antibody Formation in the Animal Body, by Dr. Frederick P. Gay, University of California, Berkeley.

Pneumococcus and Anaphylaxis, by Dr. Edward C. Rosenow, Memorial Institute for Infectious Diseases, Chicago, Ill.

Transfer of Immunity through Colostrum, by Dr. L. W. Famulener, Research Laboratory, Department of Health, New York City.

Anaphylactic Reaction in Pellagra Patients by the Inoculation of Watery Extract of Spoiled Maize, by Mr. Guido Volpino.

Zur Frage der Paratyphus-Erkrankungen, von Dr. S. von Unterberger, St. Petersburg.

Phenomena of Anaphylaxis in Pellagra Patients Inoculated with a Watery Extract of Spoiled Maize, by Prof. L. Pagliani, Turin, Italy.

The following members of the congress joined in the discussion: Dr. Wm. H. Park (New York City), Prof. Frederick P. Gay (Berkeley, Cal.), Dr. A. D. Hirschfelder (Baltimore, Md.).

The president, Prof. Theobald Smith, declared the section adjourned, since the further proceedings of the section would be merged with those of Section VIII.

FRIDAY, SEPTEMBER 27—2 P. M.

A joint session of Sections I and VIII. The session was called to order by Dr. Henry G. Beyer, the president of Section VIII.

The following papers were presented on the general subject of hookworm and hookworm diseases:

Biologie de l'Ankylostoma Duodenale Dubini, par les Drs. M. Breton et L. Bruyant (Institut Pasteur de Lille).

Number of Treatments and Number of Full Doses of Thymol Administered in 61 Hospital and 22 Home-cured Cases of Hookworm Infections, by Dr. Charles Wardell Stiles, professor of zoology, and George F. Leonard, first assistant, Hygienic Laboratory, United States Public Health Service.

Proportion of Males to Females in the American Hookworm (Necator americanus), Based on 13,080 Hookworms from 102 Cases, by Dr. Charles Wardell Stiles, professor of zoology, and W. L. Altman, assistant, Hygienic Laboratory, United States Public Health Service.

Der Infektionsweg bei Strongyloides und Ankylostomum, von Prof. Dr. F. Fülleborn, Hamburg.

Das Oleum chenopodii anthelmintici gegen Ankylostomiasis im Vergleich zu anderen Wurmmitteln, von Dr. W. Schuffner und Dr. H. Vervoort, Leipzig-Borsdorf.

Uncinariasi od Anchilostomiasi, by Prof. E. Perroncito, Turin.

Control and Eradication of Hookwork Disease, by Maj. Baily K. Ashford, United States Army.

Distribution of the Hookworm Disease, by Dr. W. S. Rankin, Raleigh, and Dr. Hiram Byrd, Jacksonville.

Methods for the Eradication of Hookworm Disease, by Dr. John A. Ferrell, Raleigh.

A Study of the Hemoglobin in its Relation to the Number of Hookworms Present, by C. W. Stiles and George A. Wheeler.

The following members of the congress joined in the discussion: Dr. W. H. Schultz (Washington, D. C.), Dr. Claude A. Smith (Atlanta, Ga.), Dr. Charles W. Stiles (Washington, D. C.), Dr. S. T. Darling (Ancon, Canal Zone).

Reports of discussions as given to the secretary will be found in the transactions of this section.

Respectfully,

Dr. D. L. HARRIS, *St. Louis, Mo.*
Dr. F. M. MEADER, *Syracuse, N. Y.*

MONDAY AFTERNOON, SEPTEMBER 23, 1912.

SOME EXPERIMENTS UPON THE NATURE OF THE VIRUS OF RABIES.

By Dr. DANIEL WARREN POOR and Dr. EDNA STEINHARDT, Department of Health, New York City.

Most of the experimental work on rabies has been with the virus as it occurs in the brain and spinal cord. In this situation it is closely associated with the elements of the nerve tissue. Comparatively little has been done with the virus as it occurs in the salivary glands, where it is presumably in a more or less free state. In our work, which has been confined to the gland virus almost exclusively, we had two objects in view. First, that of determining, in a measure, to what extent the association of the nerve tissue affected the various physical tests for determining the nature of the virus, and, second, that of comparing the physical properties of the virus in the two situations; this with the idea of noting any differences which might be found suggestive of the parts of a cycle.

Two methods have been used for obtaining the virus, the submaxillary glands from the carcasses of dogs brought to the laboratory with clinical rabies being used in both instances. In the first method, after removal of the fibrous sheath, the glands were immersed in sterile neutral glycerin and allowed to stand in the ice-box for from 6 to 12 days. Although virus may be extracted from the intact glands, it was found that more was removed when the glands were cut in pieces with a sharp razor or scissors. The clear supernatant glycerin, slightly colored by hemoglobin, is then pipetted off. This is usually found to be sterile. The glycerin containing the virus is next placed in collodion sacs and the glycerin removed by dialysis in running physiological salt solution. One and a half hours are usually sufficient for the removal of the glycerin from 4 or 5 c. c. of the glycerin virus. In this way it is possible to obtain a sterile suspension of the virus in physiological salt solution. Microscopical examination of this fluid shows it to be an exceedingly clear liquid with practically nothing demonstrable in the way of formed cellular elements. Virus obtained in this manner will subsequently be referred to a glycerin-extract virus.

In the other method the glands, after being cut, are placed in distilled water and subjected to a vacuum of 29 inches of Hg for an

hour. The pieces of the glands were then placed in an ordinary meat press and the remaining fluid pressed out. This is centrifuged and the supernatant fluid added to the water in which the glands were aspirated. It may be noted that the aspiration fluid alone was found to contain the virus, but more was present on the addition of the pressed-out juice. By this method a suspension of the virus is obtained in distilled water which is stronger than the glycerin virus, but which is not sterile and which contains fragments of gland cells, blood cells, etc. Subsequent experiments showed that bacteria and formed tissue elements could be removed by passing it through a Berkefeld filter. This virus will be referred to as aspiration virus.

That the virus in the central nervous system is in a less extractible or less free condition than in the glands would appear from the following observation:

Glycerin extracts of the glands of 32 dogs whose brains were positive to the Negri test were virulent in 71 per cent of the cases.

Eleven fixed virus brains, similarly tested, gave virulent extracts in only 36 per cent of the cases, and four street virus brains were all nonvirulent. When one considers that the brain is the culture medium for the rabies organism, which is present in much greater numbers in this situation than in the glands, one would expect a greater number of virulent brain extracts unless, as is undoubtedly the case, the virus is intimately associated with the nerve cells. Indeed, the virulent extracts from the brain virus might be accounted for by minute particles of the brain substance being torn off by the action of the glycerin (the brain being a more delicate tissue than the gland), or by the extraction of the virus from the blood and lymphatic vessels and spaces.

That the action of the glycerin on the glands is mainly that of a sucking out of the virus from the tubules is seen from the following experiment: The glands from two rabid dogs, which had given a nonvirulent glycerin extract, were removed from glycerin and ground up in a mortar with salt solution, a difficult operation owing to the tough and slippery constitution of the gland. This emulsion proved to be quite virulent. On the other hand, in some glands much virus was present in the ducts, as it was possible by a second extraction with fresh glycerin to remove virus which produced rabies with a short incubation.

FILTRATION.

In 1903 Remlinger[1] first showed that fixed virus was filterable. He emulsified the entire brain of a fixed virus rabbit in 400 c. c. of water and filtered the emulsion through a Berkefeld V under pressure. Ten rabbits were inoculated with from ½ to 1 c. c. each of the filtrate. Three of these rabbits, or 30 per cent, developed rabies.

The following year, Marie, using three different Berkefeld candles, was unable to pass the virus through in any instance. In the same year (1904), however, Bertarelli and Volpino[2] successfully filtered fixed virus through a Berkefeld V five times out of seven trials. They failed, however, to pass it through a Chamberland F. Celli and Du Blasi[3] had similar results. In 1904, also, De Vestea[4] made extensive experiments on filtration. He used fixed virus, and prepared the emulsions with great care, emulsifying the brains with the aid of quartz sand. He filtered with from two to three atmospheres pressure, and inoculated his animals with large amounts of the filtrate, i. e., ½ to 1 c. c. each. His results were as follows:

	Experiments.	Virulent filtrates.	Per cent.
Berkefeld V	19	14	75
Berkefeld N	1	1	
Chamberland F	8	2	25
Chamberland B (filtrate from Chamberland F)	1	0	
Maasen filter (filtrate from Berkefeld)	1	1	

The literature contains very little regarding the filtration of gland virus. In one instance, a virulent filtrate was obtained by Bertarelli and Volpino, who passed it through three layers of paper. It is also recorded that the virus in human saliva was passed in one instance through a Berkefeld candle.

Our experiments were made with Berkefeld V and N, Chamberland F and B, and with a collodion filter. The aspiration virus from the glands of from two to four dogs were used in each experiment. The results were as follows:

	Experiments.	Virulent filtrates.	Per cent.
Berkefeld V	4	4	100
Berkefeld N	1	1	
Chamberland F	4	3	75
Chamberland N	2	0	0
Collodion	2	0	0

In the collodion and the first Chamberland B experiment the virus used unfortunately proved to be quite weak. In the second Chamberland B experiment, however, a strong virus was obtained and the animals inoculated with the filtrate failed to show symptoms of rabies after a lapse of 6 weeks.

In order to get some idea of the amount of virus held up by the filter a series of dilutions of the fluid to be filtered was made as follows: Dilutions of 1 to 4, 1 to 8, 1 to 10, 1 to 20, and 1 to 30. It was found that the average incubation of the guinea pigs inoculated was increased in a surprisingly regular manner according to the degree of the dilution of the virus. For example, the dilution of

1 to 4 gave an incubation of 9⅓ days, as against 8⅔ days for the undiluted virus, an increase of ⅔ day only. A dilution of 1 to 30 gave an incubation of 10⅓ days, as compared with 8 days for the original virus, an increase of 2⅓ days. The average duration of incubation, then, may be taken as a rough index of the dilution of virus. All of the guinea pigs inoculated with the Berkefeld filtrates developed rabies. That more of the virus passes through after saturation of the filter is seen from the following experiment: A small Berkefeld V candle was used. The first 5 c. c. which passed constituted the first filtrate, the next 12 c. c., the second filtrate. The four guinea pigs inoculated with the first filtrate developed rabies with an average incubation period of 21 days. Those inoculated with the second filtrate developed in 12½ days. Those with the unfiltered material, diluted eight times, developed in 9½ days and, with undiluted control, in eight days. Comparing the incubation of the pigs injected with the second filtrate, 12½ days, with that of the pigs injected with the control diluted 1 to 8, 9½ days, it is fair to assume that in this case the virus was diluted by filtration more than eight times. Again in the finer Berkefeld, grade N, the average incubation of the pigs injected with the second filtrate was 15½ days, and that produced by the virus diluted 1 to 20, was only 11½ days. In a further attempt to determine the dilution caused by filtration, a Berkefeld V candle was shaved to about one-half its thickness. In this case, a weak virus, diluted 1 to 20, gave an incubation of 17 days; while the filtrate from the shaved filter gave 16 days, practically the same, so that it may be assumed that the shaved filter diluted the virus about 20 times. The filtrates from the Chamberland filters gave correspondingly increased incubation. Thus, in one test, two out of four pigs inoculated developed rabies with an average incubation of 33 days, as against 8⅓ days for the control. In a second test, two out of five pigs developed, with an average incubation of 47 days, as against 11 days for the control. The filters were tested with a suspension of pyocyaneus bacilli, which was mixed with the virus to be filtered. In no case did the bacilli pass through. Comparing now our results with the filtration of gland virus with those obtained by others in the filtration of the fixed brain virus one may infer that the greater regularity with which the gland virus passes (that is 100 per cent in the Berkefeld as against 75 per cent, and 75 per cent in the Chamberland F as against 25 per cent obtained by De Vestea) is due to the freer condition of the virus as appearing in the glands. That the organism is not necessarily smaller in this location is seen from the fact that the fixed virus did pass the Chamberland filter and, even in one instance, according to De Vestea, the Maasen filter.

When one considers further the greater number of organisms in fixed virus, the greater care used by De Vestea in preparing his emulsions,

i. e., the grinding up with quartz sand and the larger amount inoculated in his animals, ½ to 1 c. c., as against ¼ to ⅓ c. c., in our animals, the above conclusion seems all the more apparent. Whether this would indicate that the central point of the Negri body may be the true rabic parasite—the outer portion being a degeneration product of the nerve cell—we are at present unprepared to say. The following points are to be considered in this connection: First, the structure known as the complete Negri body could not pass the filter. Second, some of the minute inner cell structures might pass through. Third, these small central structures might easily exist free in the glands and escape identification. In this connection, it is interesting to note that, working in conjunction with Dr. Robert Lambert, we have been able to produce inclusions closely resembling the outer portion of Negri bodies, by allowing normal nerve cells to slowly degenerate in plasma at 37° C., according to Harrison's technique for the growing of tissues.

ATTEMPTS AT GROWING THE VIRUS.

In the first method tried, the spinal cord of a fixed virus rabbit four days after subdural inoculation was used. At this time the virus has reached the cervical end, but has not extended to the lumbar extremity. The cord was quickly removed from the canal by the Oshida method, and blocked into previous sterilized paraffin of 46° C. melting point. The whole block was then immediately solidified in ice water. In this way a more nearly anaerobic condition was obtained, a condition considered by Marie to be desirable. At the end of 10 days, not only had the virus not extended to the lower end, but had died out in the cervical end.

Attempts were then made to grow the virus, or at least to get a line on its viability by making use of the technique of Harrison's method of tisue growing. It was found that apparently the brain cells retained their vitality at incubator temperature for several days; in one distance as long as 21 days. This was inferred from the perfect staining of the Nissl bodies. However, in spite of the ganglion cells remaining alive, small portions of the fixed virus brains embedded in plasma, agar, and in simple saline solution, lost their virulence after seven days at 37° C.

On the other hand, in the only instance in which street virus brain was tried, it was found that the virulence was retained after eight days at 37° C.

Portions of normal guinea pig brain inoculated with weak emulsion of fixed virus showed no virulence after six days. Normal brain was also in a similar manner inoculated with gland virus, but here also there was no evidence of virus at the end of six days. Unfortunately, in this experiment a glycerin extract virus was used which

proved to be very weak. From our subsequent work, as will as from clinical observations, we would conclude that the most promising virus to use for this purpose, would be the strong aspiration virus freed from bacteria by passage through a Berkefeld filter. This would avoid the objection to brain virus for the cultivation of the rabic organism, made by Marie,[5] on the ground that at incubator temperature the brain tissue develops substances detrimental to the virus.

MICROSCOPICAL.

The glycerin extract dialyzed in distilled water or in salt solution, even after concentration through a collodion sac, gave a product which, while containing the organism, showed remarkably little in a way of formed elements of any kind. The aspiration virus, when filtered through a Berkefeld candle, showed many small granules, evidently from the secreting cells of the glands. Both of these viruses were examined with the dark field (1/12 and 1/16 lenses and No. 4 ocular) and in the preparations stained by Giemsa's stain.

Although very minute granules were found, we were unable to identify them as organisms.

An attempt was made to agglutinate the granules with an antirabic serum but without definite result.

COMPARISON OF BRAIN AND GLAND VIRUS.

These two viruses were compared, with the idea of noting any difference that might exist suggestive of a different physical form in the two situations. The tests were made with reference to the effect of (1) Rapid drying; (2) Drying and heat; (3) Heat; (4) The effect of certain chemicals; (5) Viability; (6) Dialysis.

(1) *Rapid drying.*—It has been known for some time that brain virus could be dried rapidly and retain its virulence, but it has been quite generally supposed that the gland virus rapidly lost its virulence upon drying.

An emulsion of brain virus made with distilled water and dialyzed for two hours was spread in a thin layer and dried in a vacuum of 29 inches Hg over H_2SO_4. After 16 hours it was completely dried. Inoculated into guinea pigs, it produced rabies in five to six days, the same as in the control kept in the ice box. The same technique, applied to two aspiration gland viruses in distilled water from two different dogs, produced a like result, the pigs inoculated from this dried virus contracting rabies in nine and one-half days identically with the controls.

(2) *Drying and heat.*—This emulsion of fixed virus and a sample of glycerin gland virus were dialyzed in distilled water for an hour. Very thin layers of each were evaporated to dryness while exposed

to 37° C. for 6 hours. In each case the virus was killed while the controls were fully virulent.

(3) *Heat.*—Thermal death point:

48°–50° C.

10 minutes	F. V. weakened.
	Gl. V. weakened.
½ hour	F. V. very much weakened, only one out of three animals developing.
	Gl. V. killed.

60° C.

10 minutes	F. V. exper. lost through disappearance of the animals.
	Gl. V. killed.
½ hour	F. V. killed.
	Gl. V. killed.

(4) *Effect of chemicals.*—A 1-1000 solution of $HgCl_2$ apparently killed both viruses.

A 1-1000 solution of HCl killed the brain virus and markedly weakened the gland virus, only one pig out of three contracting rabies with a prolonged incubation. MgO_2, in the strength of ¼ gm. to 4 c. c. of the virus, produced but little effect on either virus.

(5) *Viability.*—Gland virus aspirated in distilled water was kept in an ice box at 45° F. for 15 days, at the end of which time it had become offensive through bacterial contamination. It was then filtered through a Berkefeld V candle, a filtrate being obtained which produced rabies with an incubation of 14 days. This filtrate was then kept at room temperature and exposed to the light for 45 hours. At the end of this time the virulence was completely lost. An emulsion of fixed virus in distilled water, exposed to the same conditions for the same length of time, was markedly weakened, the incubation of the injected animals being increased to 10 days, i. e., five days longer than the controls. Exposure to light and room temperature for four days destroyed the virulence of the brain emulsion. This experiment gives but a rough comparison, as there were undoubtedly many more organisms present in the fixed virus emulsion than in the gland virus filtrate. In another experiment, the Berkefeld filtrate, from an aspiration gland virus kept in the ice box for nine days, had lost its virulence, while the unfiltered virus, kept in the same manner for the same length of time and then filtered, was shown to be virulent. This is in accord with the experiments of De Vestea on brain virus. He found that the filtrate of fixed virus died out in the ice box within a week, while the original retained its strength for a long time.

(6) *Dialysis through the collodion sac.*—Novy has shown that dialysis kills fixed rabic virus apparently through the extraction of certain salts and that the time required depends on certain factors, such as the thickness of the emulsion, rate of flow of the water, etc.

Our results were similar to his, though not identical with them, probably owing largely to the fact of our using much stronger emulsions.

We found, e. g., that the dialysis of 2 c. c. of either brain or gland virus in 200–300 c. c. of standing water had but little effect after 18 hours, but that dialysis of the gland virus in running water for 18 hours killed it. Brain virus, on the other hand, while it was markedly weakened, was not completely killed. Dialysis for 42 hours killed the fixed virus emulsion used by us. In the dialysis experiment, there were many more tissue elements, as well as organisms, in the brain virus emulsion used, than in the glycerin extract gland virus, which undoubtedly accounts for the longer time required for killing the former virus.

An interesting reverse experiment was the following:

Some of the filtrate from a Berkefeld V candle was evaporated in a vacuum over H_2SO_4 to one-fifth its bulk, the operation requiring four hours. The control, in a narrow tube sealed with paraffin, was placed in the apparatus so that conditions of light and temperature would be the same. Three guinea pigs were inoculated from the concentrated virus, as well as the control, and also the concentrated virus diluted to its original volume. The result was that while the pigs inoculated with the control died with an average incubation of 19 days, those from the concentrated virus developed only after a period of 30 days, while only one pig from the concentrated virus subsequently diluted developed after 19 days.

This suggests a harmful concentration of salts such as is believed by Harris[6] to cause the reduction of virulence in the Pasteur cords.

CONCLUSION.

In conclusion, we wish to emphasize the following points:

(1) The advantage of using the gland secretions in the study of rabies, for the reason that they contain the organism in a condition freed from tissue cells. This is an advantage for the microscopical study of the virus, for the study of its physical properties, and for its use in growing experiments.

(2) The two easy methods for obtaining bacterially sterile virus from the glands.

(3) The regularity with which the gland virus passes the filters.

(4) The similarity in the nature of rabies virus in the two locations of the brain and the glands.

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[1] Remlinger, Annal. de l'Institut Pasteur, 1903.

[2] Bertarelli and Volpino, Riv. d'Ig., 15, 1904.

[3] Celli and du Blasi, Annal. d'Ig. Speriment, 1904.

[4] De Vestea, La Med. Ital., 1904, No. 13, and Annal. d'Ig. Speriment, 1905.

[5] Marie, L'Etude Experimentale de la Rage. (Doin et fils, Paris, 1909.)

[6] Harris, Journal of Infectious Diseases, May, 1912.

NATURAL AND INDUCED IMMUNITY TO TYPHUS FEVER.

JOHN F. ANDERSON, Director Hygienic Laboratory, and JOSEPH GOLDBERGER, Passed Assistant Surgeon, United States Public Health Service, Washington, D. C.

Instances of transient or even permanent natural immunity of human beings to certain infections are not unknown. Most of these are clinical observations. It has been frequently noted that of a number of persons of a family or of a community presumably equally exposed some escape. Those who have made many vaccinations for the prevention of smallpox, especially of children, are familiar with the fact that sometimes an individual may resist several repeated inoculations; this, while it may frequently be attributed to a nonpotent virus, is in some instances at least undoubtedly due to a more or less transient natural immunity to vaccinia.

An interesting instance of natural immunity to an infectious disease in the human subject is reported by Reed (1901). One of the subjects experimented upon by Reed and Carroll resisted a subcutaneous injection of 1.5 c. c. of yellow-fever blood, and later also the bites of some infected mosquitoes.

Similar examples of individual resistance of animals to experimental infection have been noted. In the course of our studies on measles we found quite a marked variation among monkeys in the susceptibility of different individuals to the disease. Marks has well brought out the variation in susceptibility of young rabbits to poliomyelitis; and Dorset, McBride, and Niles report instances of natural immunity in the hog to hog cholera. Metchnikoff and Besredka (March, 1911) report that in one of 16 experiments they failed to infect the chimpanzee with typhoid, and McCoy and Chapin (January, 1911) report that a considerable percentage of San Francisco rats were found by them to be immune to plague at a time when immunity, due to a previous attack, could reasonably be excluded. Coming to typhus, we find that Nicolle was unsuccessful in his initial attempts to infect monkeys directly from the human subject, and from his experience concluded that to obtain success the virus had to be prefaced by passage through a higher ape, the chimpanzee.

Our own work and that of Ricketts and Wilder, of Gaviño and Girard, and others, and more recently that of Nicolle himself, has shown that such prefatory treatment of the virus is unnecessary. The apparently ready susceptibility of the monkey encountered by us in our early work suggested to us that Nicolle's initial lack of success was due to the small amount of blood used, to the subcutaneous route employed by him in those inoculations, or to both combined.

Apart from these factors there appeared to us no reason to suspect natural resistance as playing a part in explaining Nicolle's negative results.

Gaviño and Girard appear to have been the first to suggest that some monkeys may be naturally immune to typhus. They reported that a monkey of the species *Ateles vellerosus* that had previously received an injection of heated typhus blood failed to present any reaction following an immunity test of 3 c. c. of blood virulent for the control. They suggest that instead of the animal having been vaccinated by the first noninfecting injection it may have been naturally immune to typhus.

Dreyer (1911) reports that in the course of his work he found one monkey (Cercopithecus?) entirely refractory. This animal showed no trace of illness, although two others treated with the same material at the same time and in substantially the same dose promptly developed the usual (typhus) symptoms. He believed himself qualified in interpreting this as a case of natural immunity. He does not state whether he tested the susceptibility of this animal a second time.

Wilder reports that a monkey that had received an injection of filtered typhus-blood serum failed to react when given an immunity test of 4 c. c. of typhus virulent blood and suggests, among other possibilities, that the animal may have been naturally immune.

Nicolle and his coworkers, in their interpretations, do not appear to have considered the possibility of a natural immunity in the monkey; we believe, however, that a critical study of their reported protocols shows that they had encountered the same phenomenon. We believe, however, that a critical study of their reported protocols shows that they had encountered the same phenomenon.

In the course of our recent work with the New York and the Mexican virus we obtained results that brought the possibility of the occurrence of a natural resistance to typhus forcibly to our attention.

We have summarized all our monkey inoculations in which the first or primary inoculation was with monkey typhus blood. The virulence of the blood used and the dose, as well as the route of inoculation employed, unless otherwise stated, was always proven. It was found that 46 monkeys were given a primary inoculation of virulent defibrinated blood and to this 8, or 17.4 per cent, failed to react. These 8 were given a second inoculation, to which 4, or 8.7 per cent, of the original 46 failed to respond. It is proper to state, however, that one of these 4 may perhaps be considered to have presented a slight suggestion of an "abortive" reaction—so slight, however, that it escaped our attention at the time of its occurrence. If

we count this as a positive reaction, we have only 3 of the 8 that failed to respond to a second inoculation; or, in other words, at least 6.5 per cent of the monkeys failed to respond to two separate inoculations with virulent blood.

Of the three clearly resistant to the second inoculation, the immunity of only two was further tested; of these, one—rhesus No. 197—although given less than half its previous dose now developed a mild though well-defined febrile reaction; the other, rhesus No. 189, presented no indication of a reaction. After this, rhesus No. 189 was subjected to five more tests. In all, between January 2 and June 29 this animal received 8 inoculations with virulent blood, ranging in amount from 3 to 14 c. c., to which no recognizable evidence of a reaction was noted at any time during the period of observation.

Of 46 animals, therefore, one (2.2 per cent) failed to respond to any of the 8 inoculations to which it was subjected.

We have summarized our inoculations in which the initial one was either unfiltered or filtered serum.

Five monkeys received a first inoculation of virulent unfiltered serum ; three of the five animals failed to respond to this inoculation. Of these three, two responded promptly to the first immunity test (second virulent inoculation), while one, rhesus No. 221, has so far resisted five successive immunity tests (6 virulent inoculations).

Seven monkeys received a primary inoculation of filtered serum; none of the seven responded to this initial inoculation. When subjected to an immunity test, however, all but two (Nos. 115a and 194) responded; in other words, two of the seven failed to react to the first injection of virulent material. One of these two (No. 194) responded to the second immunity test and the other (No. 115a) to the third.

If now we combine the results summarized in the foregoing, we find that of 58 animals, 13, or 22.5 per cent, failed to react (i. e., did not become infected) after one injection of virulent blood or blood serum; 5, or 8.6 per cent, failed to react after two injections; and 2, or 3.5 per cent, after three injections.

It is evident that a very large proportion (22.5 per cent) of monkeys possess at least a transient immunity, and it seems reasonable to consider that in about 3.5 per cent of animals the resistance noted amounts to a permanent immunity.

It may, perhaps, be objected that this is only an apparent immunity, that the resistance is simply due to a virus of low or varying virulence, to the smallness of the dose employed, the site of inoculation, or to the size or age of the animal.

It is readily conceivable that different strains of virus may differ markedly in virulence. Analogies readily suggest themselves, and the results of our inoculations with virus from human sources appear to furnish some experimental support for such a view. A summary of our inoculations with blood from human cases of typhus shows that only a small proportion, whether New York or Mexican cases, were successful.

While, as we say, it is not improbable that in these cases viruses of differing virulence may have entered as an element, we do not believe that this factor enters into the results of the series of inoculations above considered; for the inoculations in question were made with a single strain which we have successfully propagated through some 23 monkey generations, throughout which the virus, so far as we are able to discern, has maintained its original degree of virulence. The suggestion that age may enter as a factor in susceptibility has been advanced because it is held by some that children are less susceptible than adults. As a matter of fact, there is no good evidence to show that children are less susceptible to typhus than adults. It is probably true that the manifestations of typhus in a child are not in all respects like those in the adult; that is, they are not typical, but this manifestly can not be regarded as indicating a difference in the degree of susceptibility. That this and the other objections cited are not valid may be clearly inferred from the fact, first, that of two monkeys of substantially the same size and vigor, both inoculated at the same time by the same route but with different quantities of the same virus, the animal receiving the larger dose (by 50 per cent) has failed to react; and, second, as has already been noted above, an animal may react after the second or the third inoculation, although the dose may be only half as large as that given in the immediately preceding ineffective inoculation.

The existence of a more or less marked transient (or permanent) natural immunity is of great practical importance in all work on typhus. Great caution and conservatism must be observed in the interpretation of experimental results, especially negative results. We believe, too, that it may have a much broader significance and application. It will be recalled that Metchnikoff and Besredka, in their studies on antityphoid vaccination conclude that the ingestion of Bacillus paratyphoid-B may vaccinate against true typhoid. This conclusion is based on the observation that in one of two experiments a chimpanzee that had previously been infected experimentally with paratyphoid-B was subsequently refractory to infection with typhoid. Now, while the results of future work may reinforce this conclusion, the thought readily suggests itself that an occasional

chimpanzee may be met with that may be transiently or permanently resistant to infection with typhoid. Indeed, these authors themselves, in a previous communication, report that they met with only one failure in 16 experiments to infect anthropoids. We believe, therefore, that their conclusion is to some extent at least, if not altogether, invalidated.

In a discussion of the susceptibility of the monkey it is essential to have a clear understanding of what one is to consider as a typhus reaction in this animal. Following an inoculation with virulent material the monkey continues for a period varying from 5 to 24 days as if nothing had happened. As may be seen from Table No. 1, in about 90 per cent of cases the incubation period varies between 6 and 10 days.

TABLE No. 1.

Incubation period.	Number of monkeys.
Days.	
5	1
6	12
7	20
8	16
9	23
10	16
11	4
14	4
15	1
24	1
	108

At the end of this period the temperature of the susceptible animal rises fairly rapidly as a rule, sometimes gradually or at times very abruptly. The fever reaches its fastigium in 36 to 48 or 72 hours; it then continues for a variable period of 1 or 2 to 5 or more days, then defervesces. The defervescence, like the invasion, is variable; although usually gradual, it is frequently rapid or even critical. In brief, the course of the fever in the monkey is essentially like that of the fever in man.

The fever may be accompanied by loss of appetite, thirst, a ruffling of the fur, and a drooping posture; very commonly, however, even with a well-defined febrile reaction, the animal except for some slight listlessness shows hardly any outward manifestations. In other words, the fever is the only definite index of a reaction. As may be seen from Table No. 2, in about 76 per cent of the cases the fever varies in duration between 6 and 10 days.

TABLE No. 2.

Duration of illness.	Number of monkeys.
Days.	
3	2
4	1
5	1
6	5
7	9
8	24
9	21
10	17
11	9
12	6
13	3
14	2
15	1
29	1
	102

At the termination of the fever there is almost always manifest some degree of emaciation. Occasionally after the temperature has been normal for three or four days or a week it may go up a second time; such a relapse may last 5 or 7 or more days and end in recovery or death. We have met with febrile recrudescence or relapse in 4 of 103 cases.

Although in appearance a mild disease, we have thus far had 4 deaths in a total of 103 cases of typhus in the monkey. This total of cases includes 10 induced with the Mexican virus. Segregating these, we have four deaths in 93 cases of the disease induced with the New York strain (Brill's disease), a mortality notably higher than that reported by Brill in the human subject.

An animal that has presented a reaction such as above described is immune from subsequent infection. In Table No. 3 we present the results of immunity tests in monkeys that had presented typical primary reactions. It will be seen that in no instance has such an animal responded to a subsequent immunity test. Such an immunity may last a long time, as is shown by the following: Adela, a female rhesus, was originally infected by an intraperitoneal injection of 6 c.c. of defibrinated blood from a patient with (Mexican) typhus on January 11, 1910. This animal developed a marked typhus, terminating on January 29–30, 1910. Between November 9, 1911, and March 6, 1912, this monkey was given four inoculations of typhus blood, all of which it resisted absolutely, showing that it was still immune after at least two years.

Monkey No.	Date.	C.c. inoculated.	Source.	Site.	Result.
Rhesus 95	Nov. 23, 1911	3.0	Rhesus 306	Vein	–
	Dec. 8, 1911	3.5	Case 19M	Peritoneum	–
Rhesus 127	Dec. 30, 1911	6.0	Case 38M	do	–
	Jan. 1, 1912	4.0	Case 39M	do	–
Rhesus 133	Nov. 23, 1911	3.0	Rhesus 306	Vein	–
	Dec. 8, 1911	3.5	Case 19M	Peritoneum	–
Rhesus 142	Nov. 29, 1911	5.0	Rhesus 170	Vein	–
	Dec. 12, 1911	4.0	Rhesus 161	do	–
	Jan. 11, 1912	7.0	Rhesus 186	Peritoneum	–
Rhesus 158	Nov. 9, 1911	5.0	Case 1M	Vein and subcutaneous.	–
	Dec. 2, 1911	2.5	Case 16M	Vein	–
	Dec. 22, 1911	4.5	Case 26M	Peritoneum	–
Rhesus 188	Mar. 30, 1912	3.0	Rhesus 234	do	–
Rhesus 210	Mar. 30, 1912	3.0	Rhesus 234	do	–
Rhesus 306	Dec. 29, 1911	6.0	Case 35M	do	–
	Jan. 1, 1912	4.0	Case 39M	do	–
	Feb. 1, 1912	2.5	Rhesus 184	Vein	–
Rhesus 315	Feb. 1, 1912	2.5	Rhesus 184	do	–
Rhesus 316	Feb. 1, 1912	2.5	Rhesus 184	do	–
	Feb. 23, 1912	6.0	Rhesus 200, 203, 204	Peritoneum	–
Rhesus 317	Jan. 10, 1912	3.0	Rhesus 187	Vein	–
Rhesus 318	Jan. 10, 1912	3.0	Rhesus 187	do	–
Rhesus 500	Nov. 9, 1911	4.0	Case 1M	do	–
	Dec. 2, 1911	2.5	Case 16M	do	–
	Jan. 10, 1912	3.0	Rhesus 187	do	–
	Mar. 6, 1912	6.0	Rhesus 213, 312	Peritoneum	–

Ordinarily, therefore, a well-marked febrile reaction may be interpreted as typhus without subjecting the animal to an immunity test. When, however, the fever is slight or its course atypical—that is, when we have what may be designated as an "abortive" fever—this can not be construed as a typhus reaction unless the immunity test proves the animal resistant to infection, and even then not without some reserve. Should the immunity test in such cases show that resistance has not been conferred, a diagnosis of previous typhus is not permissible.

The experimental work of Anderson and Goldberger, Ricketts and Wilder, Gaviño and Girard, and more particularly that of Nicolle and Conseil, has developed a solid basis for the conclusion that the virus of typhus is present in the blood at least throughout the febrile period. The latter two workers were the first to try to determine whether the virus is present in the blood, either before the beginning of the fever or at its defervescence. As the point has important bearings, we repeated their work, and as a result concluded (1) that satisfactory evidence has not yet been adduced that the blood of a monkey infected with typhus is virulent in the prefebrile stage, and (2) that the blood of the monkey may still be virulent 24 to 32 hours after the return of the temperature to normal.

Recognition of the infectivity of the blood naturally leads to the search for the element or elements of the blood in which the virus is localized. Nicolle, Conor, and Conseil have argued in favor of an intraleucocytic localization of the virus, and believe that the red corpuscles, after one washing, are no longer infective (or only inconstantly so). We believe this to be an error of interpretation, due to

a disregard of the possibility that the monkey is not at all times susceptible to infection. In a single experiment to test this point we found that the corpuscles were infective after three washings. This would appear to suggest that the virus adheres very closely to the blood cells. We believe, however, that the real explanation is to be found, at least in large part, in the inherent defect of the method (centrifugation) employed for the separation of the virus and the corpuscles. Just as a considerable number of leucocytes are entangled and carried down by the red blood cells in centrifuged blood, so we believe the virus is carried down by the precipitated cells.

The question of the filterability of the virus, as it exists in the blood, has been the subject of considerable research, but the results recorded do not appear to be altogether harmonious. After a careful consideration of the experiments reported by others and the results of our own experiments we are of the opinion that there is no evidence to show that the virus in the blood of typhus is able to pass the Berkefeld filter and, incidentally, that virulent typhus blood contains no toxin or contains it in quantities too small to cause an appreciable increase in the normal resistance of the monkey when injected even repeatedly in the ordinary doses.

The virus in the blood is not very highly resistant. We have found that drying for 24 hours and heating to 55° C. for 5 minutes deprives it of infectivity. It may resist freezing, however, for at least 8 days. Gaviño and Girard report that the infectivity of the blood is lost after an hour's contact with phenol in 0.5 per cent solution, but that it is retained after an hour's contact with saponin in a solution of like strength.

Notwithstanding that the transmission of typhus fever by the body louse has been shown by Nicolle and his coworkers, by Ricketts and Wilder, and by ourselves, and also that the disease may perhaps be transmitted by the head louse, there are nevertheless those who believe that there may be other methods of transmission, especially by the expired air or buccal secretions.

In experiments conducted by ourselves in regard to this point we concluded that the buccal secretions are not infective for the monkey and that therefore droplet infection plays no part in the transmission of the disease. This is in distinct contrast with the method by which measles is spread, as we have shown that in that disease the virus is contained in the buccal and nasal secretions collected before and within 48 hours after the first appearance of the eruption.

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OBSERVATIONS ON A CHICKEN SARCOMA AND ITS FILTERABLE CAUSE.

PEYTON ROUS, M. D., and JAMES B. MURPHY, M. D.

[From the laboratories of the Rockefeller Institute for Medical Research.]

The present paper has to do with a sarcoma of the chicken,[1] which has been transplanted from one to another of 32 series of fowls, and in this manner has been kept growing in our laboratory for a period of nearly three years. The chief interest of the disease lies not in the illustration it affords of the behavior of transplantable tumors in the bird—a subject of which very little has been known—but in the fact that the growth's cause has been found in a filterable agent,[1,2] almost beyond doubt a living organism. The presumption would naturally be that a growth so caused is a granuloma, not a tumor: and for that reason the characters of the disease have been subjected to especially careful scrutiny.

The original or "spontaneous" growth was found in the subcutaneous tissue of a young hen and was transplanted while the host was yet alive. Histologically it was a spindle-celled sarcoma, in some parts myxomatous, in others containing giant cells of sarcomatous type, as distinct from those seen in the granulomata of the fowl, or about foreign bodies. The transplantation of the fresh tissue to other chickens was successful, and the growth was thus established for experimental purposes. In the course of repeated transmission, its malignancy has been much enhanced. Of the many hundred derivative growths, most have had the structure of a spindle-celled sarcoma. They have been made up of large, more or less attenuated, spindle cells coursing in irregular strands and supported by a scanty, vascular framework. The remaining growths have shown striking variations within the type, suggesting those which have been noted from time to time (Bashford, Lewin) in the transmissible malignant tumors of mammals. For example, the sarcoma is occasionally formed of oat-shaped or bluntly fusiform cells, or of cells almost spherical; or many giant cells may be scattered through the tissue; or there may be a mixture of all the cells mentioned, resulting in a strikingly polymorphous appearance. Only of late have such variations been prominent.[3] All the growths, histologically considered, are tumors. They can not be confused with the ordinary granulomata or with the tissue of chronic inflammation.

Macroscopically, the growth which arises after a routine implantation of the sarcomatous tissue in a fowl's pectoral muscles is a discrete, elastic mass, lenticular, spherical or ellipsoidal, which as a rule enlarges rapidly and soon projects more or less sharply from the body contour. In hosts somewhat resistant, it is especially well

defined and is often encapulated. In them it is prone to myxomatous change, being then semigelatinous. In other partially resistant hosts, it is hard and fibrous, finely striated on section, and grayish-yellow. In very susceptible fowls it invades diffusely, and is grayish-pink, homogeneous, and gristly, or more often friable. In the latter case especially it is liable to soft, central necrosis, and to extensive hemorrhages into its substance with cyst formation.

The rapidity with which the sarcoma sometimes grows is very remarkable, though, all things considered, it is not more so than in the case of certain mammalian tumors, notably a mouse sarcoma described by Ehrlich. Within three weeks after the implantation of a tissue graft less than 2 millimeters in diameter there may develop from it a mass 12 by 6 by 6 centimeters. Over 40 per cent of the cells in the more active portions of such a growth may be in process of division at one time.[4] Amitosis is much more frequent than mitosis.

The sarcoma's increase in size is usually accompanied by an invasion and replacement of normal structures. This may be beautifully seen when the growth lies in striated muscle. The neoplastic cells frequently penetrate into the individual fibers and here, multiplying and eroding, they replace the muscle substance *in toto*, though the outline of the fiber is retained. Frequently the blood and lymph vessels are entered, resulting in metastases. Over half the fowls now dying of the growth have secondary nodules in the viscera. Usually the distribution is by the blood stream, as with other sarcomata; and the lungs are affected first, later, the organs supplied by the greater circulation. The lungs are sometimes nearly replaced by coalescing nodules, and may be doubled in bulk. Metastases are frequent in the liver, heart, and ovary, and are met less often in kidney, spleen, gizzard, and bone marrow. A widespread dissemination may occur on the surface of the peritoneal cavity.

The host at first seems unaffected by the developing growth, but soon it begins to lose weight, becomes anemic and emaciated, and, in the absence of intercurrent processes, dies in coma.

These are the superficial characters of a tumor, yet in themselves they do not suffice to identify the growth as one. The essential feature of tumors, which distinguishes them from other new formations of tissue, has yet to be considered, namely, that of growth by division of the cells already neoplastic, as contrasted with growth by a pathological change in cells previously normal. Are the extension and distribution of the chicken sarcoma referable to this cause?

The problem has been studied in several ways. The direct histological evidence thus far collected would suffice to settle it in the case of any other growth. The histological character of the growth, the number of division figures, the evidence of pressure on surrounding

structures, the noteworthy invasion and replacement by a tissue which is often very distinct from that of the structure attacked, the extension of strands of the growth into the lumen of blood vessels, the casting off of cell emboli, and the lodgment and growth of these emboli at distant sites, may all here be cited as indicating growth "aus sich heraus," to use Ribbert's words. We have repeatedly found all stages in the formation of metastases by means of cell emboli. But experimental evidence is more convincing. A suspension of the fresh tumor tissue was injected intravenously into a number of normal fowls, and after some days these were killed, and the lungs examined in serial section. It was found that the sarcomatous nodules developed from tumor bits that had lodged in branches of the pulmonary artery and proliferated there, penetrating at length through the vessel coats into the pulmonary tissue. Many of the tumor emboli had failed to survive, and about these the sarcoma did not arise. By a study of the fate of numerous grafts of a single sarcoma implanted in a susceptible fowl, and removed at operation on successive days, it has been shown that the sarcomatous tissue survives transplantation to other hosts, is vascularized, and by its proliferation gives rise to the new growth. In resistant fowls the implanted tissue dies and no sarcoma arises.

It is certain then that the chicken sarcoma grows "aus sich heraus," possesses, in other words, that fundamental character by which at present we distinguish tumors. But it may well be asked, Does not the growth extend also by the infection of neighboring cells? Certainly such a possibility can not be ruled out on histological evidence alone, any more than it can in the case of the mammalian sarcomata, and the demonstration of an agent causing the growth would appear *a priori* to render such infection very likely in its case. But we have found that a number of circumstances, later to be enumerated, limit the agent's activity,[5] and to such an extent that, even by specially devised experiments, we have been unable to show that infection of the sort mentioned has any share in the sarcoma's ordinary manifestations. These are referable entirely to growth and dissemination "aus sich heraus."

A further and interesting proof that the chicken sarcoma is a neoplasm is found in the behavior of the growth in the various hosts to which it has been transplanted. For some time workers have known that there are certain conditions affecting the success of tumor transplantation, which are either entirely different from those influencing the transmission of infectious diseases or are much more precise in their effect. (L. Loeb, Schöne, Bashford, Fichera, Rous.) These conditions are largely the same ones that affect the transplantation of normal tissues. The fact is one of the most significant that

has resulted from modern cancer research, and has furnished a strong argument to those theorists who refer the cause of cancer to an intrinsic cell derangement, as distinct from an infectious agent. But it happens that the chicken sarcoma, though indubitably caused by an extrinsic agent, is markedly influenced by the conditions mentioned.

Prominent among such conditions is blood relationship, a factor which plays so large a part in the success of surgical grafting. Our original chicken sarcoma occurred in a fowl of pedigreed stock and was transplantable at first only to this fowl's immediate relatives (fowls in the relationship of half brother, half sister, uncle, and aunt). In nonrelated fowls of exactly the same breed (barred Plymouth Rock), it would not grow. Only after repeated transplantation, which resulted in enhanced malignancy, did it become less precise as regards a host. Even when last tested (eighth tumor generation), it grew best in chickens of the original strain. Despite repeated efforts it has never been successfully transferred to mammals, rabbits, guinea pigs, rats, mice), or to other birds than chickens (pigeons, ducks).

The physical condition of the host has a marked influence on the chicken sarcoma, the reverse of that obtaining for the usual infectious diseases, and similar to that noted in the case of the transplantable mammalian tissues, normal and neoplastic. An emaciating illness, instead of predisposing the host, renders it relatively insusceptible, and may cause the rapid retrogression or even the temporary disappearance of well-developed sarcomata.[2] The growth is more easily transplanted to young hosts than to old, and grows more rapidly in them, a fact already known of the transplantable mammalian tissues. By inoculations into chick embryos (seventh to tenth day), without disturbing their development, we have found that embryos are especially susceptible as hosts.[4] Some adult fowls exhibit a natural resistance that is independent of age, condition, or variety. Though apparently very suitable as hosts for the tumor, these fail to develop a growth even after repeated inoculations with active tumor tissue. In some chickens, too, the sarcoma, after growing for a while, retrogresses without evident reason, leaving the host temporarily resistant. All the types of resistance mentioned have their parallel in mammals. The histological processes about the retrogressing tumor or the unsuccessful graft are essentially similar in the case of the chicken tumor and rat and mouse tumors.[5]

So much, then, for the characters of the chicken sarcoma. They stamp the growth as a tumor in all that the word implies at this day when our conception of the neoplastic process rests, not merely on clinical and anatomical data, but on broader experimental findings. So close a correspondence between the tumor phenomena in the bird and those in mammals could hardly have been expected.

Our first attempts to determine the chicken sarcoma's cause were made without expectation that they would lead to positive results. By three methods, an etiological agent, as distinct from the tumor cells, has been demonstrated, viz, by filtration, by drying, and by glycerinization.[1, 2, 7] The fluid obtained by passing an extract in Ringer's solution of the fresh sarcomatous tissue through a Berkefeld filter (N) will give rise to the tumor; sarcomatous tissue dried *in vitro* over sulphuric acid, ground to powder, and so kept for weeks or months, will likewise cause it; and so will tissue kept for weeks *in* 50 per cent glycerin.[8] No special complexity has attended our use of these procedures. The tumors engendered by filtrate, or by the dried or glycerinated tissue, do not differ from those resulting from transplantation, except that they take, as a rule, very much longer to appear and often grow much more slowly. They metastasize, and are capable of transplantation, forming the potential source of any number of growths from each of which the agent may be obtained in quantity.

The characters of the agent are those which we associate with microorganisms;[7] and it would appear to be among the larger of the filterable causes of disease, failing, as it does, to pass through a Chamberland bougie, though it goes easily through a Berkefeld cylinder (N or V) impermeable to *Bacillus fluorescens liquefaciens*. Our repeated attempts to observe the agent directly and to cultivate it *in vitro* have thus far failed. In dried or glycerinated tissue it undergoes a gradual attenuation. In fresh sarcomatous tissue it survives repeated, rapid freezing and thawing, which reduces the tissue itself to a pulp. It is rendered inactive by heat (55° C. for 15 minutes) a little greater than that which kills the associated tumor cells (50° C.), as shown by the results of attempts to grow them *in vitro*. It is quickly rendered inactive by autolysis, by chloroform and toluol, in the proportions used to prevent bacterial growth in autolytic preparations, by 2 per cent carbolic acid, and by 50 per cent alcohol. Like the animal organisms in distinction from most of the vegetable ones (v. Prowacek) it is destroyed by high dilutions of seponin and by bile.

The relation of the agent to the disease which it causes is at present unique in pathology, for the behavior of the sarcoma is entirely referable, as already shown, to the cells composing it. Recent work has made evident some of the reasons for this.

In the first place the agent elicits of itself no noteworthy immunity. The resistance induced in fowls by retrogression of the sarcoma is very weak, is frequently transient, and its histological manifestation about a fresh graft of the sarcomatous tissue is of the sort which we have come to recognize as indicating resistance to the strange tissue as such. With the object of obtaining a more marked resistance

many chickens have been injected with gradually increasing amounts of the dried sarcomatous tissue, attenuated at first by heat. Most of these have sooner or later developed the sarcoma and died of it. The sera of the fowls which survived and of rabbits which had been similarly injected have shown only very dubious powers of neutralization when incubated *in vitro* with the agent. The absence of well-defined immunity processes directed against the agent as such explains very well why immunity processes directed against the transplanted tumor tissue as strange tissue, and present in any event, come to claim attention. Their existence in the case of this and other growths does not mean necessarily that an etiological agent other than the cells themselves must be absent. It means simply that the phenomena of resistance to such an agent, if present, are less well marked than those directed against the cells themselves.

Secondly, the agent does not act upon normal connective tissue. To bring about a neoplastic change it must have opportunity to affect connective tissue in which a proliferative reaction is occurring. A large quantity of Berkefeld filtrate containing the agent in active form, when introduced through a fine needle into normal tissue has only rarely results in a growth, and this growth develops in the track of the injecting needle, but if to the filtrate there be added a little sterile *Kieselguhr* (which produces, as Podwyssozki has shown, a profuse connective tissue reaction) tumors follow a large percentage of the inoculations, and they develop from numerous foci where the reaction to *Kieselguhr* is going on.

Third, the agent's action in producing tumor tissue by a change in cells not previously neoplastic is very slow as compared with the proliferation of these cells, once they have undergone a neoplastic change. The first few cells that become sarcomatous rapidly divide and elaborate the mass of tumor tissue. Their activity overshadows any coincident neoplastic transformation, granting, indeed, that the factor of cell derangement necessary for this be present.

The existence of these three limitations to the agent's activity will largely account for the latter's failure to take an obvious part in the tumor's ordinary growth and distribution in the host. The existence of yet other limiting factors would explain why this failure is so nearly absolute. It is to such factors also, discovered and undiscovered, that the sarcoma's failure to appear as an epidemic disease, and its total lack of infectivity in the ordinary sense, must be attributed. During the last year we have collected some 30 spontaneous chicken tumors without encountering again the picture of the sarcoma; and in our laboratory, during the last three years, there have been kept in close quarters large numbers of fowls with and without the disease, yet we have still to find an instance of its natural transmission under these circumstances.

The results of the study thus briefly summarized offer more than a suggestion as regards the etiology of malignant tumors. They afford a rational explanation, founded on an actual instance, of some of the more puzzling features of these growths. The peculiarities of occurrence of malignant growths, the importance of tissue derangement in their etiology, their growth and dissemination by means of cells, their behavior on transplantation, are quite compatible with the assumption that they are caused by an agent limited in its action by conditions somewhat similar to, but doubtless more complex than those influencing the agent causing the chicken tumor. But whether this assumption be correct, the work of the future must determine. Certainly the findings with the chicken sarcoma largely demolish the theoretical objections to an extrinsic cause for cancer.

NOTE.—Since the above article was written we have demonstrated that a filterable agent is the cause of an osteo-chondro-sarcoma of the fowl, recently propagated in this laboratory. The agent causing this growth, like that of the spindle-celled sarcoma, requires for its action an associated cell derangement, but true cartilage is laid down in the growths to which it gives rise.[9]

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[1] Peyton Rous, Jour. Exp. Med. 1910, xii, 696. J. A. M. A. 1910, liv, 1805.

[2] Ibid., Jour. Am. Med. Ass. 1911, lvi, 198; Jour. Exp. Med. 1911, xiii, 397; Proceedings Am. Philosoph. Soc. 1912, li, 201.

[3] An article dealing with these variations will shortly appear in the Jour. of Exp. Med.

[4] J. B. Murphy and Peyton Rous, Jour. Exp. Med. 1912, xv, 119.

[5] Rous and Murphy, Jour. Exp. Med. 1912, XV, 270.

[6] Rous and Murphy, Journal of the American Medical Association, 1911, LVI, 741; Journal of Experimental Medicine, 1912, XV, 119.

[7] Rous and Murphy, Jour. of Amer. Med. Assoc., 1912, LVIII, 1938.

[8] Two other methods, namely, freezing and thawing the fresh tumor tissue, and heating it at 50–53° C. allow a less satisfactory differentiation of the agent from the cells.

[9] See Peyton Rous, J. B. Murphy, and W. H. Tytler, Journal of the American Medical Association, 1912, LIX, 1793.

TUESDAY MORNING, SEPTEMBER 24, 1912.

UEBER CHOLERAELEKTIVNÄHRBÖDEN.

By Prof. ADOLF DIEUDONNÉ, University of Münich, Germany.

In der Deutschen amtlichen Anweisung für den bakteriologischen Nachweis der Cholera ist bereits ein stark alkalischer 3 procentiger Agar empfohlen, auf dem die Entwicklung anderer Keime wesentlich eingeschränkt wird. Von diesem Nährboden, dessen Elektivität auf der starken Alkalitoleranz der Choleravibrionen basiert, ausgehend, hat *Dieudonné* durch Zusatz von bestimmten Mengen Rinderblutes, das speciell auf Vibrionen wachstumsfördernd einwirkt, einen neuen Choleraelektivnährboden angegeben, durch den die bakteriologische Untersuchung auf Cholera wesentlich vereinfacht wird, und ihr Nachweis mit weit grösserer Sicherheit gelingt. Bei der Bereitung dieses Nährsubstrates werden defibriniertes Rinderblut und Normalkalilauge zu gleichen Teilen gemischt and ½ Stunde im Dampfstoff sterilisiert; die Mischung wird dann mit 3 procentigem, genau auf den Neutralpunkt eingestelltem Agar im Verhältnis von 3:7 versetzt, und das Ganze sofort in Petrischalen ausgegossen. Dabei verwendet man nach dem Vorschlag von Neufeld u. Woithe am besten 15 ccm Nährbodenmasse für je 1 Petrischale von 10 ccm Durchmesser. Wenn die Nährbodenschicht festgeworden ist, werden die Schalen geschlossen und mit dem Deckel nach unten je nach dem Feuchtigkeitsgehalt 12–15 Stunden lang im Brutschrank bei 37° aufbewahrt. Es empfiehlt sich vorher zwischen Ober- und Unterschale und ihre Wandungen kleine Streifen Fliesspapier einzulegen, sodass die Schalen teilweise offen sind und ein Ansaugen und Entweichen der Feuchtigkeit und der Abdampfstoffe (Ammoniak) erzielt wird.

Der Dieudonné'sche Blutalkaliagar hat sich bei den schr zahlreichen Nachprüfungen und in der Praxis bei Choleraepidemien bereits ausgezeichnet bewährt. Allerdings haftet ihm der Nachteil an, dass er nicht sofort, sondern erst nach einiger Zeit, im ungünstigsten Fall erst etwa 18 Stunden nach dem Ausgiessen der Platten, benutzt werden kann, weil bei sofortiger Verwendung jedes Bak-

terienwachstum, auch die Entwicklung der Choleravibrionen unterdrückt wird. Um diesen Missstand abzuhelfen, sind von verschiedenen Autoren eine Anzahl Modifikationen angegeben worden, von denen die bekanntesten, nämlich die von Neufeld-Woithe, Esch, Pilon, Hoffmann-Kutscher und Moldavan, im folgenden mitbesprochen werden sollen.

Neufeld u. Woithe suchten einen sofort verwendbaren Blutalkaliagar dadurch zu gewinnen, dass sie unmittelbar vor dem Giessen der Platten auf je 100 ccm des Nährbodens 2 ccm 10 procent. Milchsäure zusetzten behufs Bindung des Ammoniaks, bezw. zur Neutralisation eines etwaigen Ueberschusses der nach dem langen Kochen etwa noch übermässig vorhandenen Lauge. Dieser Nährboden, der nach ¼ stündigem Trocknen der Platten im Brutschrank von 60° sofort benutzt werden kann, behält aber seine Elektivität für Cholera nur kurze Zeit, da nach 24–48 Stunden die Alkalescenz infolge der zunehmenden, durch den Zusatzt der Säure eintretenden Neutralisation stark herabgesetzt wird.

Esch benutzte bei Herstellung seiner Modifikation 5 g käufliches Hämoglobin (von der Firma Marck in Darmstadt), das er in 15 ccm Normalnatronlauge +15 ccm Aqua destillata auflöste. Das Gemisch wurde 1 Stunde in Dampf sterilisiert, und davon wurden 15 ccm mit 85 ccm lackmusneutralen 3 procentigem Agar vermengt und zu Platten gegossen. Nach kurzer Trocknung bei Zimmertemperatur können die angelegten Platten bereits verwendet werden. Allerdings bemerkt der Autor selbst, dass die Elektivität seines Ersatznährbodens nicht den gleich hohen Grad wie der Originalagar erreicht.

Pilon vertritt die Auffassung, dass die anfängliche totale Wachstumshemmung des Dieudonné'schen Blutalkaliagars nicht, wie Huntemüller annimmt, auf der Ammoniakentwicklung beruhe, sondern dass durch den ursprünglich hohen Alkalilaugengehalt des Nährsubstrates die Entwicklung der Choleravibrionen unterdrückt werde. Erst wenn also die Alkalilauge durch die Kohlensäure der Luft in Karbonat umgewandelt worden sei, könne man die Originalblutagarplatten benutzen. Er suchte daher einen sofort gebrauchsfähigen Nährboden dadurch zu erzielen, dass er die Kalilauge durch Sodalösung ersetzte. Nach seinen Angaben werden defibriniertes Blut, am besten Schweineblut und 12 procent Sodalösung zu gleichen Teilen gemischt und nach 1 stündiger Sterilisierung im Dampftopf mit lackmusneutralem 4 procentigem Agar im Verhältnis 3:7 gemengt. Die frisch gegossenen festgewordenen Platten bedürfen dann vor dem Gebrauch noch einer ½ stündigen Trocknung im Brutschrank.

Einen weiteren Ersatz für den Originalagar stellt der von Hoffmann und Kutscher angegebene, getrocknete Dieudonné'-Blutalkaliagar. Er wird in der Weise gewonnen, dass man den gewöhnlichen

Dieudonné'schen Originalnährboden in Petrischalen ausgiesst und im Faust-Heim'schen Apparat trocknet. Man erhält so ein braunes, ziemlich grobkörniges Pulver, das, vor Feuchtigkeit geschützt, lange haltbar ist. Zur Bereitung des gebrauchsfertigen Nährbodens löst man 8 g dieses Pulvers in 100 ccm Wasser auf und kocht das Gemisch ½ Stunde im Dampftopf. Vor dem Giessen der Platten empfiehlt es sich, den Nährboden kurze Zeit noch im Kolben stehen zu lassen, weil sich die trüben Bestandteile dann am Boden absetzen, und das Nährsubstrat ziemlich hell und durchscheinend wird. Die frisch gegossenen, abgekühlten Platten sind ebenfalls nach kurzer Trocknung im Brutschrank bei 60° verwendbar.

Moldavan mischt Blutalkali und Agar im Verhältniss von 1:4. Die gegossenen Platten bleiben 6 Stunden (also für die Anreicherung in Peptonwasser) unbenützt bei Zimmertemperatur stehen. Nach dieser Zeit beimpft erweisen sie sich zwar schon etwas weniger elektiv als der Originalnährboden, aber günstiger für das Wachstum der Choleravibrionen, sodass letztere wenn überhaupt wachstumfähig, stets angehen.

Aus diesen Ausführungen geht hervor, dass die Herstellung dieser verschiedenen Nährmedien sich bei sämtlichen Substraten in derselben einfachen Weise durchführen lässt. Einen gewissen Vorteil dürfte die von Esch angegebene Modifikation insofern bieten, als das von ihm benutzte Hämoglobin stets vorrätig gehalten werden kann und die Aufbewahrung gut verträgt. Was das Aussehen der einzelnen Nährbodenplatten betrifft, so zeigen die des Originalagars, der Neufeld-Woithe'schen und der Pilon'schen Modifikation eine dunkelbraune Farbe und sind undurchsichtig; die Platten des getrockneten Blutalkaliagars, sowie die nach Moldavan und nach Esch hergestellten dagegen sind hell und ziemlich gut durchscheinend. Eine wesentliche Aufhellung auch der obigen 3 Nährmedien erzielten Haendel u. Baerthlein, auf deren umfangreiche, im Kaiserlichen Gesundheitsamt durchgeführte Nachprüfungen sich unsere kritische Wertung des Originalagars und seiner Modifikationen im Wesentlichen stützt, durch Verwendung älteren, defibrinierten Blutes, das einige Zeit im Eisschrank aufbewahrt worden war. Bei sämtlichen Nährböden mit Ausnahme der Neufeld-Woithe'schen Modifikation blieb die Elektivität für Cholera bei Aufbewahrung im Eisschrank lange Zeit gut erhalten. Dagegen erscheint eine längere Aufbewahrung des Blutalkaliagars im Kolben wenig angezeigt, weil durch das notwendige, wiederholte Kochen die Nährböden rasch weich und brüchig werden.

Was nun das Wachstum der Cholera auf den erwähnten Nährsubstraten betrifft, so entwickeln im Allgemeinen auf sämtlichen Nährböden ältere wie frisch isolierte Kulturen ziemlich grosse, flache, rauchbraune, bezw. auf dem Esch'schen Blutagar graubraune Ko-

lonien, die auf den Pilon'schen Platten am üppigsten wachsen. Einen gewissen Nachteil zeigt indessen der mit Milchsäurezusatz hergestellte, sowie der nach Moldavan gewonnene, indem trotz genauer vorschriftsmässiger Herstellung in einzelnen Fällen auch das Wachstum echter Cholera unterdrückt wird. Die Agglutinabilität der Choleravibrionen, die nach der Angabe einzelner Untersucher bei dem Wachstum auf den blutnährböden vermindert sein soll, ist wohl etwas verzögert wegen der Klebrigkeit des Materials, aber nicht in dem Masse, dass dadurch die Diagnosestellung leidet. Die chloleraähnlichen Vibrionen wachsen auf dem Esch'schen und dem Pilon'schen Nährboden ebenso gut wie echte Cholera, während sie auf dem Dieudonné'schen Originalagar spärlicher gedeihen, auf den anderen Modifikationen verschiedentlich überhaupt nicht zur Entwicklung kommen.

Nach den vergleichenden Untersuchungen von Haendel u. Baerthlein über die entwicklungshemmende Eigenschaften der Nährböden anderen, insbesondere Stuhlbakterien gagenüber ergaben sich zwischen den einzelnen Nährsubstraten doch recht beträchtliche Unterschiede. Wenn man die verschiedenartigen Kokken in Abrechnung bringt die zwar auf allen Nährböden ziemlich häufig, wenn auch spärlich zur Entwicklung kommen, aber durch das Aussehen ihrer äusserst feinen Kolonien sich leicht von echter Cholera unterscheiden lassen, also ohne praktische Bedeutung sind, so blieben die mit den Fäces darmkranker und gesunder Menschen beimpften Platten beim Dieudonné'-Agar in 50–60 procent, beim Neufeld-Woithe-Agar in 87 procent, beim getrockneten Dieudonné'-Agar in 42 procent, beim Esch-Agar in 5, 7 procent, beim Pilon-Agar in 22 procent und endlich bei der Moldavan-Modifikation in 65 procent der Fälle steril. Wir sehen also, dass hinsichtlich der Elektivität die Neufeld-Woithe'sche Modifikation an 1., der Dieudonné'sche Originalagar und der nach Moldavan an 2., der getrocknete Dieudonné'sche Nährboden an 3. Stelle stehen, während bei der Pilon'schen und Esch'schen Modifikation die Verhältnisse weniger günstig liegen. Die innerhalb 24 h zur Entwicklung gekommenen Bakterien sind auf dem Nährboden nach Neufeld-Woithe nur Vibrionen und Alkaligenesstämme; auf dem Originalagar, dem getrockneten Agar und den Modifikationen nach Moldavan, Pilon und Esch wachsen ausser diesen Bakterienarten noch dem Protens und der Coligruppe zuzurechnende Kulturen, wobei auf dem Esch- und dem Pilon-Nährboden speziell die Coli-Bakterien reichlich vertreten sind und zu Verwechselung mit Cholerakolonien führen können. Mittels des Pilon'schen Nährsubstrates wurden noch vereinzelt Paratyphus-Stämme isoliert.

Die Prüfung der verschiedenen Nährböden durch Aussaat aus Stühlen, denen neben anderen Bakterien jeweils auch Choleravi-

brionen in fallenden Menge zugesetzt waren, zeigte, dass auf sämtlichen Blutalkalinährböden im Allgemeinen während der ersten 24 Stunden die Choleravibrionen entweder die anderen Bakterienarten glatt überwuchern, oder doch so weit zur Entwicklung kommen, dass ihre weitere Isolierung mit Hilfe von Agarplatten gut gelingt. Von praktisch wichtiger Bedeutung hinsichtlich der Abkürzung der Choleradiagnose ist dabei die Feststellung, dass sich häufig bei entsprechend reichlichem Cholerawachstum von den ersten Stuhlplatten schon die quantitative Agglutination und in manchen Fällen auch der Pfeiffer'sche Versuch ausführen lassen. Bei spärlicher Entwicklung der Cholerakolonien oder gleichzeitigem, reichlichem Wachstum von choleraähnlichen Vibrionen oder Alkaligenes, bezw. Proteus auf den Platten, wie dies in der Praxis verschiedentlich vorkommen dürfte, empfiehlt es sich aber dringend, erst mit frisch angelegten Agarkulturen die betreffenden Reaktionen vorzunehmen. Erwähnt sei auch, dass, was für die Weiterzüchtung der isolierten Stämme von Bedeutung ist, auf dem Blutalkaliagar in der Regel keine Reinkulturen von Cholera bei der Züchtung aus dem Stuhl sich entwickeln, wie man auf den ersten Blick häufig glauben könnte; denn die übrigen Stuhlbakterien kommen zwar nicht zur Entwicklung, sie werden aber auch nicht abgetötet und können bei Abimpfung selbst von einer isolierten Cholerakolonie auf andere Nährböden nach längerem Stehen der neuen Nährsubstrate leicht zu schwerer Verunreinigung und Schädigung der betreffenden Cholerakultur führen.

Zusammenfassend ergibt sich also, dass die verschiedenen Blutalkaliagar-Nährböden den bisher in der Choleradiagnose gebräuchlichen Nährsubstraten wesentlich überlegen sind. Durch ihre Benutzung vereinfacht sich die Isolierung der Vibrionen aus verdächtigem Material ganz bedeutend und die Choleradiagnose lässt sich in den meisten Fällen nach kürzerer Zeit stellen wie bisher. Unter den angegebenen Elektivnährböden hat sich der Dieudonné'sche Originalagar am zuverlässigsten und besten bewährt.[1] Zu berücksichtigen ist allerdings, dass er nicht sofort, sondern erst etwa 18 Stunden nach dem Giessen der Platten gebrauchsfähig ist.

Den ersten, verdächtigen Fällen Bis Firrdman zunächst eine der erwähnten Modifikationen benutzen, unter denen der getrocknete Dieudonné'sche Originalagar, oder die Modifikation nach Esch und Pilon als geeignet erscheinen, während die Nährböden nach Neufeld-Woithe und nach Moldavan nicht die gleich grosse Sicherheit bieten, da sie wegen ihrer hohen Elektivität in seltenen Fällen auch auf die Entwicklung der Choleravibrionen zu stark hemmend einwirken. Für die Untersuchung der weiteren Fälle wäre indessen der Dieudonné'sche Originalnährboden angezeigt.

Zum Schluss sei noch in Kürze auf zwei von Ottolenghi, bezw. von Kraus angegebene Methoden eingegangen, welche einen Ersatz des

Anreicherungverfahrens von Choleravibrionen in Peptonwasser bringen sollen. Nach den Angaben von Ottolenghi wird frische Ochsengalle durch Papierfilter filtriert, und das Filtrat mit 3 ccm einer 10 procentigen Lösung von kristallisiertem Natriumkarbonat, sowie mit 0., 1 Kaliumnitrat versetzt. In die einzelnen Reagensröhrchen werden dann je 5 ccm der Mischung abgefüllt und sterilisiert. Gegenüber dem Peptonwasser soll die Galleanreicherung auch bei spärlichem Vorhandensein von Choleravibrionen im Stuhl noch gute Resultate zeitigen, ferner auf die verschiedenen Stuhlbakterien und auch auf andere Keime stark entwicklungshemmend einwirken. Endlich gestatte dieses Verfahren die Verwendung ziemlich grosser Fäces-Mengen.

Kraus benutzt den schon von Dieudonné in seiner ersten Veröffentlichung angegebenen flüssigen Blutalkalinährboden. Je 100 ccm neutraler Bouillon werden mit 25 ccm Blutalkalilösung gemischt: Diese Blutalkalibouillon wird zunächst 3 Stunden bei 50° und dann 24 Stunden bei 37° gehalten, hierauf in Mengen von 5 ccm auf Reagensröhrchen aufgefüllt und beimpft. Kraus bemerkt ausdrücklich, dass dieser Nährboden unbedingt durch einen Vorversuch auf seine elektiven Eigenschaften geprüft werden muss. Die fertige Lösung ist längere Zeit hindurch haltbar.

Mit der Gallenanreicherung von Ottolenghi erhält man nach den Mitteilungen von Haendel und Baerthlein in manchen Fällen vielleicht etwas bessere Resultate als mit der Peptonwassermethode. Jedenfalls ist aber das Galleverfahren dem Peptonwasser nicht in dem Masse überlegen, dass sich seine ausschliessliche Einführung an Stelle des Peptonwassers empfehlen würde. Wie bei der Peptonwasseranreicherung ist auch bei der Benutzung der Galle eine frühzeitige Untersuchung nach etwa 4–6 Stunden erforderlich. Die Methode von Kraus hat sich nach Haendel und Baerthlein in verschiedenen Fällen bewährt und gegenüber dem Peptonwasserverfahren ganz wesentliche Vorteile gezeigt. Allerdings ist, wie ja Kraus selbst hervorhebt, bei der Herstellung jeder frischen Lösung diese vor ihrer endgültigen Verwendung auf ihre Elektivität zu prüfen. Nach Schürmann und Abelin ist der Nährboden für die Choleradiagnose nicht brauchbar, da eine Anreichung der Choleravibrionen nicht beobachtet wurde.

[1]Auch bei verschiedenen Epidemien, z. B. in Apulien, hat der Nährboden gute Resultate ergeben und er scheint sich besonders auch zu Massenuntersuchungen zur Feststellung von Bazillenträgern zu eignen.

DISCUSSION.

Dr. E. LIBMAN, New York: Several years ago there was introduced by two of the assistants in the laboratory of the Mount Sinai

Hospital, Drs. Bernstein and Epstein, a method by means of which it is possible to have always in hand blood ready for use in cultural work. The method is, in brief, the following:

Blood is obtained at the slaughterhouse in flasks containing a certain amount of formalin and of ammonium oxalate. When this is received at the laboratory it is diluted with two parts of salt solution. After standing in the ice box for 24 hours it is ready for use. One adds one-fifteenth (more may be used) volume of the blood to any medium. Bacteria of all kinds grow at least as well on these blood-media as on those prepared with fresh blood.

The blood remains bright red for a varying length of time—after three or four weeks. We make a fresh supply every three weeks and are always ready for work requiring the use of blood in media.

EGG-AGAR AS CULTURE MEDIUM FOR CHOLERA SPIRILLA.

Dr. Charles Krumwiede, Jr., Research Laboratory, Department of Health, New York, N. Y.

In the preceding paper Dr. Dieudonné has given a detailed account of his medium and the various modifications which have been suggested.

During the summer of 1911 we used the original Dieudonnê medium extensively. Where examinations were being constantly made, it seemed ideal. Where, however, examinations were infrequent, it was unhandy because of the difficulties in its preparation. The necessity of waiting overnight before the plates could be used was removed in Pilon's modification. The necessity of obtaining blood as a basis for the medium still remained. This may be very inconvenient to obtain. For this reason we substituted eggs as a basis for the medium. The resulting medium is made as follows:

A. Whole egg and water a. a., sodium carbonate cryst. 12 per cent. Mix in equal parts; steam in Arnold sterilizer for 20 minutes.

B. Meat-free agar, viz, peptone, 1 per cent; salt, ½ per cent; agar, 3 per cent.

Mix A, 30 parts and B, 70 parts, while the agar is boiling hot. Pour medium thick plates, allow them to stand open for 20 to 30 minutes to dry, and inoculate by surface streaking.

In making the egg mixture the egg and water should be thoroughly shaken, the alkali added, and again thoroughly shaken. The thicker parts of the egg may be removed by filtration through a thin layer of cotton. The agar requires no change of reaction, and need not be filtered more carefully than to remove the coarser particles.

On this medium the cholera colonies are distinctive. Examined by transmitted light, they have the appearance of being deep in the agar,

and have a peculiar hazy, far-away appearance, due to an indefinite halo about the colony. When growth is more vigorous, viz, on longer incubation, this halo becomes surrounded by a zone of clearing. In practice, fishing from this type of colony has yielded cholera, and from this type alone. The only exception is in the case of cholera-like vibrios whose colonies are identical. Comparing this medium with the Dieudonné medium, the latter is somewhat more selective. This is more than offset by the fact that if growth of fecal bacteria should occur on the egg medium, the presence of even one cholera colony is immediately evident because of its distinctive characteristics.

The various blood media are not completely selective, nor does the cholera colony on any we have tried approach in distinctiveness the colony as found on the egg medium.

The advantages of the medium are the prompt availability of the ingredients, the ease of preparation, and the distinctiveness of the cholera colonies. For infrequent examinations, the first two are of great importance. As a routine medium it is economical. Ten eggs are sufficient for over 300 plates.

THE USE OF CALCIUM CARBONATE IN SOLID MEDIA FOR THE DIFFERENTIATION OF SUGAR-FERMENTING BACTERIA, ESPECIALLY OF THE COLON-TYPHOID GROUP.

Dr. A. J. Bendick, College of Physicians and Surgeons, Columbia University, New York City.

Media containing lactose with litmus as an indicator for acidity have been extensively used for growing the colon bacillus and differentiating it from closely allied organisms. This type of medium is well exemplified in Wurtz's lactose litumus-agar, which consists of a 1 per cent lactose-agar colored with litmus. These media have several defects, chiefly due to the rapid diffusion of the acid, causing a general reddening of the adjacent medium. This necessitates having plates with few colonies and examining and counting while the colonies are still small. Also gas formation often occurs, ruining the plate.

To overcome these disadvantages, media consisting of stiffer agar have been devised, on which surface smears are made. This is the type of the Conradi-Drigalski medium, which consists of a special nutrient 3 per cent agar, to which crystal violet is added as an inhibitor for less resistant organisms than the typhoid bacillus.

With the intention of limiting the diffusion of the acid formed by the splitting of the lactose I began to experiment by adding various alkalies to the medium. But such alkalies as NaOH and Na_2CO_3, when added in sufficient quantities, had a deleterious effect on many

of the organisms, and, besides, colored the medium an intense blue, which completely masked the production of alkalies, which production is of value in identifying typhoid colonies and those of the organisms of putrefaction.

A neutral agar was desired in which the acid produced by the fermentation of the sugar would be neutralized in order to prevent its diffusion. This result can best be obtained by using an insoluble alkali or alkaline salt.

The simplest and most efficient of the insoluble alkalies seems to be calcium carbonate—precipitated chalk. Being an impalpable powder, it is readily distributed through the medium, it exerts no inhibition on the organisms, is readily obtainable everywhere, and is inexpensive. Furthermore, the chalk, in combining with the acid, is dissolved; hence, acid-forming colonies are surrounded by a clear zone. This clearing of the medium is a valuable aid in recognizing acid-forming colonies.

The medium consists of:

	Gm. or c. c.
Agar	15
Liebig's extract	5
Salt	5
Peptone	10
Lactose	20
Calcium carbonate	4
Litmus solution	100
Water	1,000

The agar, Liebig's extract, salt, and peptone are dissolved in 1 liter of water, either in the autoclave or over the free flame. This is then cleared with the whites of two eggs and filtered through cotton. No titration or adjustment of reaction is necessary. The medium should then be flasked, 250 c. c. to a flask preferably of 500 c. c. size. One gm. of powdered calcium carbonate is then added to each flask, and the whole sterilized in the autoclave. Finally, to each flask is added 25 c. c. of Kahlbaum's aqueous litmus—according to Kubel and Thiemann—(or an equal quantity of a solution of azolithmine); and 5 gm. of chemically pure lactose. Tube by pouring direct from flasks to tubes, keeping contents well mixed. Sterilize in an Arnold sterilizer for 15 minutes on three consecutive days.

In using this medium either surface smears may be made on plates or the tubes inoculated and poured. For most uses, the poured plates give best results. To obtain a uniform distribution of the chalk throughout the medium, the tubes should be rolled rapidly to and fro between the palms of one's hands, and then by alternately depressing and raising the plugged end of the tube, combining this with a rotary motion. This mixing should be done as soon as tubes

are melted and while still hot. They are then cooled to 42° C. The may then be inoculated and poured.

Inoculated plates may be incubated 14 to 48 hours at 37° C. from 2 to 5 days at room temperature. Usually 18 to 24 hours at 37° C. gives best results.

Acid production in this medium is shown by:

1. Dissolving of the chalk about the colony due to its combination with the organic salts.

2. Reddening of the colony due to the litmus.

3. Microscopically, by the deposition of crystals of the calcium salts of the organic acids.

Differentiation between colon and typhoid colonies on this medium is readily made.

COLON COLONIES.

1. *Surface.*—These are large disk-shaped colonies, slightly depressed in the media. There is a variable amount of clearing about them, due to the solution of the chalk. The extent of clearing depends on the length of time the plates are incubated. Microscopically, on focusing up and down, the chalk is seen to be dissolved just below the colony and about its periphery. Crystals of the calcium organic acid salts are usually seen.

2. *Deep.*—These are rounded or spindle-shaped, showing a very distinct clearing of the chalk for a considerable area about the colony.

TYPHOID COLONIES.

1. *Surface.*—These are large white or bluish-tinged colonies showing no clearing of the chalk. Microscopically, the amorphous granules of the chalk are seen to be both within and about the colony. No crystals of the organic salts are present.

2. *Deep.*—These are distinct colonies lying embedded in the chalk without solution of the chalk occurring.

For isolating the typhoid bacillus from feces, sewage, or contaminated water 1 per cent lactose and 1 per cent saccharose may with advantage be substituted for the 2 per cent lactose. Plates should be incubated 14 to 20 hours at 37° C. Suspected typhoid colonies should be fished and inoculated into Hiss tube media or other suitable media for identification. I have on several tests isolated typhoid bacilli direct from the feces without enrichment.

The advantages of this medium are:

1. Neutralization of the acid as it is produced.

(A) Crowded or well-diluted plates may be used with equal advantage.

(B) The period of incubation is not limited.

(C) Acid formation is more clearly shown and its extent may be gauged.

2. Simplicity of the medium:

(A) Stock meat extract may be used by simply adding chalk, lactose, and litmus.

(B) The medium is neutral in reaction to litmus without titration or adjustment. The acidity of meat extract is neutralized by the chalk, giving a neutral agar on which slight alkalinity or acidity is readily shown.

This type of medium may be used in growing and identifying any organism in which the fermentation of any sugar is the base of its differentiation. For some organisms, such as the pneumococcus and streptococcus, meat infusion agar may be substituted for the meat extract agar. Any of the sugars may be used instead of the lactose. The percentage of sugar may be varied from 1 to 5 per cent.

SPECIAL CULTURE MEDIA FOR PURE CULTURE OF AMŒBÆ FOUND IN INTESTINES OF MAMMALS.

ANNA W. WILLIAMS, from the Division of Laboratories (director, Wm. H. Park), Department of Health, New York City.

In February, and again in December, 1911, the writer published reports of growing amœbæ isolated from the intestines of mammals on tissue culture media without the presence of other microorganisms. So far as the author knows, these are the only reports of growing, successively, strictly pure cultures of amœbæ. These pure cultures are comparatively easily obtained. The conditions are, simply, strict asepsis in removing the tissues and sufficient controls in transplanting the cultures to be sure of being rid of the ubiquitous air germs, of those growing originally with the amœbæ, and, lastly, of those sometimes circulating in the blood of the animals chosen for the tissue media.

In carrying on the work further, some interesting points have come to light in regard to the life history of these organisms which may be mentioned now, though the study is incomplete. Only one of the strains of amœbæ originally used has been chosen, and its life cycle has been studied in these pure cultures under varying conditions (amœba 11524 from Manila). This culture is now in its seventieth culture generation on brain media.

The brain medium among the three tissue media found suitable—i. e., brain, liver, and kidney—seems to be the best for abundant and continuous growth; therefore, this has been used exclusively in the further studies.

A most important part in regard to these tissue media is that they afford a good opportunity of studying amœbæ in cultures under conditions at least approaching some of the more important ones found in the intestines, such as continued high temperature combined with much moisture, some lack of oxygen, and the presence of cell-division excitants. These conditions have apparently been little considered by previous investigators, and not at all by some of the more recent ones, in their culture studies, though such conditions must obviously be of marked influence in the life history of any protozoan: and, if so, it seems to the author that to compare so-called strict parasitic forms, seen in preparation directly from the intestines or tissues of mammal hosts, with culture forms grown under conditions far removed from those obtaining in these mammals, is, to say the least, illogical.

Until such comparative studies are made the question of the relationship between the so-called strictly parasitic and pathogenic amœbæ and the so-called free-living forms, among which have been included by all of the most recent writers the culture amœba, must remain an open one.

It is not surprising that these writers have obtained only the results with their cultures that they have reported, for they have grown their amœbæ on the surface of more or less rapidly drying agar, with one or two varieties of bacteria, at a temperature much below that of the body. Under these conditions one would expect the organisms to pass rather quickly into simple protective cysts containing one nucleus and showing few other changes. And this, according to nearly all descriptions, is just what they do.

One investigator, Latham (1911), considered at least some of the intestinal conditions and he has reported some suggestive results from his culture experiments. Briefly, his work is as follows: He worked with two culture strains which came from Manila (numbers not designated) and which he called *Entamœba coli*. He studied the life cycle of these strains with certain auxetics (Ross) or substances supposed to be capable of inducing division in living cells. He used chiefly tyrosin, leucin, and skatol. He states that on an alkaline agar medium containing 0.2 per cent tyrosin a complete life cycle is passed through in about three days, as compared with the four-days' cycle on Musgrave & Cleggs's medium. In three days all of the amœbæ of a given generation have encysted. Then a large number of cysts produce eight daughter forms inside of them, and the amœbulæ come out of their cysts and start a new generation on the same medium. This has been seen through five generations. This important communication, unfortunately, does not go into details, but, until such a time as it may be disproved, it must be regarded as evidence that

amœbæ in cultures may show schizogony similar to that described for *Entamœba coli* in intestinal contents.

Now, as to the original work. In the first place, the fact must be emphasized that the strain of amœba used in these studies, as well as many other culture strains, grows readily, abundantly, and continuously at high temperature (38° C.). Whitmore states that he was unable to get his culture to grow above 26° C. Most other authors simply say they grow their cultures at room temperature, and the others do not mention temperature. Growing Amœba 11524, then, at continuous high temperature (38° C.), with an adequate supply of moisture, and in a mass of brain tissue which supplies sufficient food and partial anaerobiosis, the following results are obtained: In the first 48 hours the amœbæ (planted from a number of trophozoites) grow and divide rapidly. They spread over the surface of the brain mass and penetrate a certain distance within it. Spreads fixed moist in Zenker's fluid, and stained with Delafield's hematoxylin show trophozoites somewhat similar to those described for culture forms by other authors, except many more mitotic figures are seen if the amœbæ happen to be well fixed and stained. In three days there are a number of forms showing two fully developed nuclei and occasionally one showing three; the organisms are larger and may be somewhat vacuolated, and the chromatin about the periphery of the nucleus is much larger in amount. In four days there are many very large forms which show two nuclei, and some three and four. The peripheral nuclear chromatin in some has markedly increased. These forms are apparently in good physical condition, as on subculture they seem to be normally motile, and they divide in a short time into daughter amœbæ. A number of forms have encysted, and among these a goodly number show two nuclei. Even so far we find that the results are quite different from those reported by Whitmore, Walker, Craig, and others for their culture forms. They all state that the cysts in their cultures contain only one nucleus. In five days, unless some substance is added to excite the amœbæ to renewed growth, there are more encysted forms on the surface of the growth, while, a little below the surface of the brain mass, some motile forms have begun to show distinct changes in the nucleus and cytoplasm—the peripheral chromatin appears to be passing into the cytoplasm, and the caryosome is distinctly smaller. The chromatin in the cytoplasm appears to be collecting in small masses, some about the periphery of the cytoplasm; such forms, as you may see from the photograph, present an appearance similar to that described from the exogenous sporulation of *Entamœba histolytica*. The fate of these various forms in pure cultures is still under observation.

Now, if to a three-day pure brain tissue culture some bacterium suitable for food for the amœbæ be added in small enough amounts to prevent an immediate overgrowth of the bacterium at the high temperature used, the amœbæ grow and divide with marvelous rapidity, and in such cultures we find, in the next two or three days, the majority of the amœbæ containing two, three, and four nuclei, some containing five, and a few containing six nuclei. Unfortunately I have not yet been able to get good photographs of these, partly because these forms take up the stain so readily and partly because the nuclei are often not in the same plane. In these cultures many forms have large vacuoles, and a series of forms has been observed corresponding to that described by Schaudinn and others as autogenous conjugation in *Entamœba coli*. In these cultures, also, definite cysts containing four and five nuclei have been found.

These observations are being continued. I wish only to state at present that, so far, these studies starting with pure cultures of an ameba obtained from intestines of man have lead us to the following conclusions:

1. That when conditions of temperature, anaerobiosis, moisture, and food supply in certain culture amœbæ are varied, so as to be more in accord with conditions found in the intestines and tissues of amœba hosts, appearances may be produced which seem to be similar to many of those described as important in the entamœba group.

2. That this fact opens up anew the question of the relationship between the "parasitic forms" (Entamœba) and the "free-living forms" (Amœba).

DISCUSSION.

Capt. CHARLES F. CRAIG, Medical Corps, United States Army: These observations of Dr. Williams are suggestive and important as showing the effects of environment upon cultural amœbæ. However, I do not believe that they prove that cultural amœbæ are entamœbæ, or true parasitic amœbæ. According to her description of the morphology of this amœbæ in the brain media, forms were observed which resembled slightly all three entamœbæ of man—*coli*, *histolytica*, and *tetragena*. Of course, such an observation as this is most confusing and, I believe, indicates that the developmental forms showing such appearances are abnormal and have no relation whatever to true parasitic amœbæ. Practically all protozooloists who have studied sufficient material agree in considering the cultural and parasitic ambœbæ as entirely different, and the modifications in structure detailed by Dr. Williams are not sufficient to prove that this cultural amœbæ has been transformed morphologically into an entamœbæ. The nuclear structure, even in the four-nucleated stage, as shown in the photographs, is entirely different from the nuclear

ructure of any of the entamœbæ and still approaches closely the ypical nuclear structure of the same cultural amœbæ when grown on Musgrave's medium.

However, I think that Dr. Williams should be congratulated upon aving succeeded in obtaining pure cultures of amœbæ, certainly a reat step in advance in the study of this class of organism.

THE BACTERIAL EXAMINATION OF WATER.

By EDWIN O. JORDAN, Professor of Bacteriology, University of Chicago, Chicago, Ill.

When the purpose of a bacterial water examination is to determine he occurrence, recency, or degree of bacterial contamination of a potentially dangerous character, it is generally held that the quantitative estimation of *B. coli* furnishes the most satisfactory evidence. Konrich,[1] to be sure, in an elaborate critical summary, maintains that the coli test is no more than an unnecessary complication of the older modes of procedure, but the general experience of water analysts with this method, extending in this country over 20 years, is strongly in its favor. It is true that the presence of *B. coli* in water is not always due to contamination with material of human origin, but many observers have shown that the number of colon bacilli in a water does not rise above a certain level—usually fixed as about 1 per c. c.—unless exposure to fecal contamination has existed. Savage,[2] for instance, was led by his study of a large number of water supplies in Wales to conclude that even in surface waters exposed to animal contamination from adjacent fields and grazing grounds the ratio of *B. coli* is less than 1 in 2 c. c., unless other sources of pollution exist. In the United States the water of the Great Lakes is practically free from *B. coli*, even in 50 and 100 c. c. samples, except in the immediate neighborhood of human habitations. In the vicinity of large cities, like Chicago and Milwaukee, a zone of colon bacilli may extend at least as far as 5 or 6 miles from shore.

In whatever way the presence and relative abundance of *B. coli* in water may be interpreted there can be no doubt that the absence of this organism from quantities as large as 100 c. c. gives more direct and convincing evidence of the bacterial harmlessness of the water than any other method, chemical or bacteriological.

For the earliest recognition of the importance of the quantitative estimation of *B. coli* in water, as well as for a practical numerical method, we are indebted to Theobald Smith. The fermentation tube method devised by him in 1892 is to-day the basis of some of the most widely used procedures.

In the course of some water examinations, I have had occasion to make comparative tests of certain of the media in current use or

recommended for the quantitative estimation of *B. coli*. One th has been widely employed in this country is the lactose bile mediu An obvious advantage of this method is the inhibition of a numbe of water bacteria thought to be nonsignificant, including g producing bacteria other than *B. coli*. This facilitates isolation o *B. coli* and is also asserted to give a higher value to the presumpti test. A disadvantage apparently not so generally recognized is th inhibiting effect of the bile upon genuine colon bacilli. It is a mitted that the bile exerts some restraining effect upon the "weake cells of this species. The last report of the committee of the Amer can Public Health Association on "Standard methods of wat analysis" (1912, p. 88), states that "it has been found that th lactose bile medium is slightly inhibitive to *B. coli*, especially attenuated form." In point of fact, inhibition also of fresh isolated strains of *B. coli* occurs to a noteworthy degree. This sup pression of freshly isolated fecal strains in pure culture on bile ag has amounted, in my observations, to from 30 to 65 per cent. A series of tests made with lactose bile fermentation tubes on fres sewage in 1:100,000 dilutions has given positive results in only abou 45 per cent of the samples in which *B. coli* was present, using lactos broth enrichment tubes, plating, and complete identification as a standard. In a word, the use of the bile medium may lead to th suppression of at least half of the viable cells of *B. coli* present i freshly isolated fecal cultures and in fresh sewage.

It may be noted here that an increased percentage of positiv results will be obtained from lactose broth, used as an enrichmen medium for *B. coli*, if a number of colonies are fished after plating and especially if the contents of the fermentation tube are replate after an initial negative result. In one series of observations, made on Lake Michigan water, *B. coli* was not infrequently isolated o replating from lactose fermentation tubes which, in the first trial had given negative results. Approximately one-fourth of the tube examined in this way finally yielded typical *B. coli*. It is well known also that *B. coli* does not always produce typical colonies on litmus lactose agar, and that further identification tests are necessary.

I have also used Endo medium for comparison with lactose broth plating two samples, of 5 c. c. each, direct in this medium, and comparing with ten 1 c. c. samples in lactose broth fermentation tubes. Ninety cubic centimeters of Lake Michigan water, examined in this way, have yielded, by the lactose broth enrichment method (plating in litmus lactose agar and subsequent identification), 34 cultures of *B. coli*, while the parallel samples on Endo medium have given 36 identified cultures. Not all the colonies on Endo medium resembling typical *B. coli* prove to be *B. coli* on further examination. Of

102 colonies fished and examined, 72 proved to be *B. coli*. Twenty-nine picked as negative were all negative. On the other hand, 12 out of 61 colonies picked as doubtfully resembling *B. coli* turned out to be characteristic *B. coli*. As a presumptive test, therefore, simple enumeration of the colonlike colonies on Endo plates is no more reliable than the lactose bile or lactose broth methods. In this respect my experience agrees with that of Frost[3] rather than that of Schürer.[4]

In general, it would seem that a plating method would be preferable to a dilution method. The Endo medium is much more valuable for direct plating than litmus lactose agar, since overgrowth occurs but seldom, and the colony differentiation is sharper. In an attempt to combine these advantages with rapid identification, I have obtained excellent results by picking colilike colonies from the Endo medium, and transferring to Russell's medium and gelatin. Nearly all colonies giving a positive reaction in Russell's medium are typical for *B. coli* in gelatin, but a few of uncertain systematic position (8 in 116) liquefy gelatin. As already stated, some of the colonies on Endo medium, that are unlike *B. coli*, or that doubtfully resemble the latter, yield positive reactions when transferred, but further investigations should permit a pretty accurate estimation of the proportion of such forms.

To summarize briefly: Bile media are not properly selective, since a considerable and varying proportion of the cells of *B. coli* do not develop in them. This is true not only of media, to which natural bile is added, but also, although to a lesser degree, of media such as MacConkey's, which contain the purified bile salts. Simple lactose broth in fermentation tubes, although not open to objection on this score, permits the development of so many gas-producing bacteria of uncertain sanitary significance that plating out and identification will generally be considerd necessary. Direct plating on Endo medium allows the use of fairly large amounts of water, does not inhibit any viable cells (so far as comparison with ordinary nutrient agar indicates), and leads to characteristic colony formation in the great majority of cases. Transfer of selected colonies to Russell's medium and gelatin permits a fairly rapid and complete identification. Compared with the more roundabout and time-consuming method of enrichment in lactose broth and subsequent plating, the procedure here outlined gives almost exactly the same proportion of positive results, and is simpler and quicker.

[1] Klin. Jahrb., 1910, 23, p. 1.

[2] Jour. of Hyg., 1902, 2, p. 320.

[3] Bull. No. 78, Hyg. Lab., U. S. Pub. Health and Mar. Hosp. Service, pp. 73–134.

[4] Ueber den Nachweis des B. coli im Flusswasser, Inaug. Diss., Gottingen, 1910.

DISCUSSION.

Prof. Dr. Gärtner (Jena) sagt, dass in Deutschland noch immer die Untersuchung der Lokalität an erster Stelle stehe. Die Abwesenheit von Colibacillis gibt nur an, dass zu Zeit keine Infectionsgefahr vorliegt, aber sie sagt nichts für die Zukunft. Ausserdem ist das atypische Coli ebenso häufig im Darm von Menschen und Tieren vorhanden als das typische. Das Bact. coli hat in manchen Fällen eine grosse Bedeutung, in anderen nicht.

Dr. F. L. Rector (Brooklyn, N. Y.). During the past year some work has been done in my laboratory, using a medium of dried ox-bile peptone, lactose agar, and neutral red. This is used in direct planting work, and on this medium the colon shows as a distinct purplish red colony, the color shading off into the denser medium. Streptococci may show red, but their colonies are not so large, nor is the characteristic color present. In using this medium as a check with litmus lactose agar, it was found that 55 or 60 per cent of the colonies isolated, not all of which were characteristic, proved to be colon, while only 18.5 per cent of those on litmus lactose agar were colon.

E. O. Jordan. I think there can be no difference of opinion on the point raised by Prof. Gärtner. In passing judgment on the character of a water-supply knowledge of the environmental condition is essential. Often examination of the local surroundings gives all the information needed. It is not necessary to analyze a river water to determine whether it is polluted with sewage if one can see the sewage flowing into it. Under some conditions, however, analytical evidence is an important aid. It is sometimes uncertain, from simple local inspection, whether a water-supply is or is not contaminated; the degree of self-purification occurring in a flowing stream can not be determined by inspection alone; in the Great Lakes, mere ocular examination can not determine the distance from shore to which dangerous contamination may extend. There are conditions, then, when bacterial examination may aid in forming judgment as to the character of a water. Such bacterial examinations can not replace the environmental inspection; they presuppose it.

Dr. Wm. H. Park. The practice in America is nearly in accord with the opinions of Prof. Gärtner. In New York City the description of the source of the water supply is always considered together with the chemical and bacterial examination. In surface waters a number of colon bacilli might not be considered very suspicious, while in well or spring water the same number would be very significant.

CULTIVATION OF MALARIAL PLASMODIA IN VITRO.

Prof. C. C. Bass, Laboratory of Tropical Medicine and Hygiene, Medical Department, Tulane University, New Orleans, La.

This was a stereopticon demonstration. A paper discussing the technique for the cultivation of malarial plasmodia was published by Drs. C. C. Bass and Foster M. Johns, in the Journal of Experimental Medicine, Volume XVI, No. 4, 1912.

DISCUSSION.

Capt. CHAS. F. CRAIG, Medical Corps, United States Army: When I first read of the cultivation of the malarial plasmodia by Dr. Bass, I am frank to say that I was very skeptical, but without my requesting them, the doctor very kindly sent me a complete set of stained preparations containing examples of the complete schizogamy of the æstivo-autumnal plasmodium, and I am prepared to state that he has undoubtedly grown them through one generation, and in my preparations another generation was apparently beginning.

I believe that the successful cultivation of the malarial plasmodia will greatly aid us in the elucidation of many still unsolved problems connected with these parasites. It should be of great value in the study of species and perhaps will settle once and for all time the question of the occurrence of a quotidian and tertian æstivo-autumnal plasmodium, which is still a matter of controversy among students of malarial disease. The early development of the gametes and the actual form of the parasites which cause long-term relapses, may possibly be studied in these cultures, for it is reasonable to suppose that latent or resistant forms would develop even more numerously in such cultures than in the patient's blood. In this way we may be able to decide whether parthenogenesis, intracorpuscular conjugation, or the development of the plasmodici in small numbers is responsible for relapse. The method should be of great value for teaching purposes, as in this way it will be possible to supply classes with malarial preparations, even in regions where the disease does not occur. It is needless to say that if these parasites can be cultivated through many generations, great therapeutic results may be obtained by testing the effect upon the cultures of various remedial agents, and in this way we may be able to discover a specific for malaria more efficient and less disagreeable than quinine.

I was specially impressed with the fact that in the culture the polymorphonuclear leucocytes were phagocytic, for in actual malarial infection it is generally the monouclear leucocytes that are most phagocytic.

TUESDAY AFTERNOON, SEPTEMBER 24, 1912.

A CRITICAL REVIEW OF THE BACTERIOLOGY OF HUMAN LEPROSY (WITH SPECIAL REFERENCE TO THE CHROMOGENIC AND NON-CHROMOGENIC ACID-FAST STRAINS).

CHARLES W. DUVAL, M. D., Tulane University, New Orleans, La.

(From the laboratories of Pathology and Bacteriology.)

Since the discovery by Hansen in 1872 of an acid-fast bacillus in the leprous lesion to which he ascribed an etiological rôle, numerous investigators have reported success with its artificial cultivation. It may be stated, however, that many of the cultures which have been isolated and described by various workers so differ in their acid-fast property and their morphological features from the Hansen bacillus of the tissues that no one of them has been universally accepted as the specific organism of leprosy, although many of these cultures are said to have induced experimental lesions similar to human leprosy.

A review of the literature would seem to show that three, and possibly four, apparently different germs have been cultivated from the leprous lesion and described as the casual agent of the disease, namely: (1) A non-acid-fast streptothrix which becomes acid fast by passage through the rat (Kedrowski), (2) an acid-fast chromogenic bacillus (Clegg), (3) a chromogenic non-acid-fast and acid-fast streptothrix (Ross and Williams), and (4) an acid-fast nonchromogenic bacillus which grows in vitro only in the presence of the amino acids (Duval).

In the experience of the author two types of acid-fast organisms may be cultivated from the leprous lesion which have distinct characteristics—one, an extremely pleomorphic bacillus, variable in its ability to retain the stain after the ordinary methods of decolorization, and multiplies profusely on all media as a moist lemon or orange-colored growth; the other, a permanently acid-fast bacillus, which grows only upon special foodstuffs and apparently does not produce pigment. These two types probably include many of the cultures which have been described from time to time as the leprosy organism, since the chromogenic variety is often a non-acid-fast diphtheroid, streptothrix, etc., depending upon growth conditions.[1] These tinctorial and morphological variations of the pigment pro-

cer might account for the bewildering number of "stages" for
e Hansen bacillus of some European writers.

Kedrowski's organism, which he cultivated from the leprous nodule
.d regarded as the specific bacillus of leprosy, he describes as a non-
id-fast streptothrix, which becomes permanently acid fast after a
journ for several weeks in the tissues of the rat. He advances the
ieory that the acid-fast rods seen in human leprosy represent but a
age in the developmental cycle of a single pleomorphic species.

More recently Bayon[3] described a non-acid-fast diphtheroid which
e obtained from a leper that behaved in a manner similar to
Kedrowski's culture; i. e., the initial growth from the human tissues
vas non-acid fast until passed through the rat, after which it
hanged into an acid-fast bacillus. He concludes that not only
s his culture identical with Kedrowski's, but also that it is the
ause of human leprosy, basing his argument upon specific reac-
tions obtained with human leper serum and also upon the production
of lesions in the laboratory animal. It is reasonable to suppose that
Kedrowski and Bayon were dealing in the beginning with a mixed
culture which became purified by animal passage, thus accounting
for the disappearance of the pleomorphic non-acid-fast forms after
the culture was recovered from the tissue of the experimental animal.
The non-acid-fast diphtheroid and streptothrical forms, which were
present in their original cultures from the human tissue, can be
accounted for in no other way.

Though I have not compared Kedrowski's acid-fast organism with
my nonchromogenic strain, it is possible that they are the same,
since the isolation and cultivation of both were obtained with the
products of tryptic digestion. Kedrowski used these nutrients, with-
out apparently knowing it, in the form of placental extract, because
he does not mention why he used placenta in preference to other
media, or that it contains the amino acids. Whether Kedrowski's
organism, since it has become permanently acid fast, is identical with
my nonchromogenic strain can be determined, of course, by a com-
parative study of the cultures.

In regard to the chrome-producing organisms which have been
isolated from the leprous lesion and thought to be of etiological sig-
nificance, Clegg's[4] culture is perhaps the most important. He an-
nounced his success in the cultivation of a chromogenic bacillus which
he obtained from the specific lesion in a large series of lepers in
the Philippines. Multiplication in each instance occurred in the
transferred tissue bits when planted with amœbæ and their symbionts,
and pure cultures were subsequently secured on the ordinary labora-
tory media as a moist, profuse, yellow pigmented growth, by heating
at 60° C. for 30 minutes to kill out the symbionts.

Ross and Williams[5] have also reported upon the successful cultivation from the leprous nodule of an organism similar to that of Clegg's, together with which they found streptothrical forms and acid-fast diphtheroids.

Still other chromogenic cultures similar to Clegg's have been cultivated from the leper by Duval[6] in Louisiana, Brinkerhoff, and Currie[7] in Hawaii, Rivas[8] in Philadelphia, Thompson[9] in Australia, and Wellman[8] in California.

I have compared the original chromogenic culture of Clegg with those isolated independently by other workers, and have found them identical, except the Ross and Williams strain. Careful scrological tests with immune sera tend to show that they are all closely related. Furthermore, the serum tests prove conclusively that these chromogenic cultures are not related to the nonchromogenic strain cultivated from the leprous lesion by me in 1910;[10] in other words, they are distinct species.

In a previous paper[11] I regarded the nonchromogenic and chromogenic cultures as one and the same organism; attributing the subsequent alteration in morphology of the culture, its increased rate of growth and production of pigment, as within the possibilities of a species which had become adapted to an artificial environment. The lesions which were induced in the monkey with the chromogenic culture seemed further proof of its specificity, because they were indistinguishable from the human lesion. However, I have since determined that lesions similar to leprosy can also be induced in this animal with many of the well-known saprophytic acid-fast species.

That the chromogenic strain exists in the lesion of certain types of leprosy, there can be no doubt, even where the overlying skin is apparently intact, and also in the internal organs at autopsy. Again, the chromogenic species is also the predominating organism in the leprous abscess, and undoubtedly accounts for the orange-yellow color so characteristic of the pus from this type of lesion. Of course, it is well known how ubiquitous are the saprophytic acid-fast species, it being possible to isolate them from almost any source. Their occasional occurrence, therefore, in the open-skin lesion of leprosy is to be expected, but to find them so frequently is difficult to understand, if we accept that they are in no way concerned in the disease.

As stated in a former publication,[11] the chromogenic variety has been cultivated from 14 out of 29 cases of leprosy in Louisiana; while the nonchromogenic strain was recovered from 8 cases. Since it is more difficult to cultivate the nonchromogenic species, especially where the two exist in the lesion, this probably accounts for the larger percentage of cases yielding the chromogenic variety. Further-

ore, the subplants of the chromogen remain for many generations ithin the morphological variations and staining properties of the onchromogenic type, which would not lead one to suspect that he as dealing with two distinct species of acid-fasts.

Prior to 1910, all the attempts to cultivate the Hansen bacillus hrough successive generations were carried out upon media containng the whole protein. That the initial multiplication of the leprosy acillus in removed tissue bits has been obtained by a number of workers there can be no doubt. The failure has been to perpetuate the culture through any number of generations.

The relationship of the leprosy organism to the tissue cells *in vivo*, and its ability to multiply in digested pieces of excised leprous tissue, explains, in my opinion, its failure to grow outside of the animal body upon a medium which does not contain the products of tryptic digestion. It also explains why transplants from a culture which contains both the chromogen and nonchromogen to ordinary media have resulted ultimately in the growth of the pigment producer; the nonchromogenic type, or true Hansen bacillus, which I believe it is, failing to multiply as soon as removed from the amino-acid nutrient.

Experiments with the amino-acids [10] as a culture medium, and the behavior of B. lepræ in digested bits of leprous tissue, establishes the fact that the organism requires the products of tryptic digestion for assimilation, and is unable to attack and break down the whole protein. Where multiplication has been noted, the medium undoubtedly contained these important nutrients. Practically in all my successful attempts to cultivate the specific organism, the transferred pieces of the leprous tissue were responsible for the growth. Multiplication occured whenever, for one cause or another, the tissue underwent digestion, and, conversely, did not occur if the tissue protein remained unaltered short of amino-acid dissociation. Usually the digestion was due to the action of some contaminating microorganism. I have repeatedly shown this to be the case by purposely adding to the removed bits of leprous nodle some one of the protein-splitting bacteria, and almost without exception the acid-fast rods have multiplied as soon as digestion was well advanced.

SUMMARY.

The various acid-fast cultures which may be cultivated from the human leprous lesion fall into two groups: (1) A nonchromogenic bacillus, cultivated with difficulty, and growing *in vitro* only upon special foodstuffs, (2) a pigment producing pleomorphic organism, which is likewise difficult to cultivate through the first generations, but subsequently multiplies readily on all media.

Under certain conditions the individual bacilli of the chromogenic species are diphtheroid, streptothrical, and nonacid fast, while those of the nonchromogenic species are always acid fast and maintain in general the morphological variations common for the tubercle family.

Serological tests differentiate between these two acid-fast types and indicate that the slow-growing nonchromogenic variety is the etiological factor in human leprosy, and that the chromogenic strain belongs to the group of saprophytic acid-fast bacteria.

Since we frequently encounter in the leprous lesion diphtheroidal, streptothrical, and other forms of saprophytic species capable of changing *in vitro* under defined conditions, it is easy to explain the "stages" described by Kedrowski and also Bayon in the developmental cycle of the Hansen bacillus.

I believe that the specific organism of leprosy in culture as well as *in vivo* is nonchromogenic, acid fast, and thus far has been cultivated *in vitro* only upon an amino-acid medium.

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[1] Jour. Infec. Diseases, 1912, XI, p. 116.
[2] Ztschr. f. Hyg. u. Infectionskr, 1901, 37, p. 52.
[3] Tr. Soc. Trop. Med. & Hyg. 1912, 5, p. 158.
[4] Philippine Jour. Sc. 1909, 4, p. 403.
[5] Scientific Memoirs of the Government of India, 1911, 42, p. 1.
[6] Jour. Exper. Med. 1912, 15, p. 292.
[7] U. S. Government Reports, 1910.
[8] Personal communication.
[9] Australian Med. Gazette, 1912, 31, p. 209.
[10] Jour. Exper. Med., 1910, 12, p. 649.
[11] Jour. Exper. Med., 1912.

DISCUSSION.

Prof. CREIGHTON WELLMAN, New Orleans: I wish to call attention to the success obtained by us in New Orleans using the placental-extract-agar devised by myself as a medium for the cultivation of strictly parasitic or feebly saprophytic bacteria. When I first devised this medium, I thought that the idea was a complete novelty. I have learned since, however, that Kedrowski suggested in 1902 the use of placental juice, although my medium and its method of preparation is very different from his original suggestion. In conclusion, I wish to say that we in New Orleans at present hold that careful consideration is due the nonchromogenic acid-fast leprosy organism, discussed in the paper just read.

INFLUENZAL MENINGITIS, EXPERIMENTAL AND CLINICAL.

MARTHA WOLLSTEIN, M. D., Rockefeller Institute for Medical Research, New York City.

The more general use of lumbar puncture has made it evident that influenzal meningitis is a distinct and not infrequent form of seropurulent inflammation of the cerebrospinal meninges. Its clinical picture is indistinguishable from the meningococcal and pneumococcal forms of meningitis, and it is only by cultural demonstration of *B. influenzæ* in the fluid obtained by lumbar puncture that the diagnosis can be positively made. The mortality rate of influenzal meningitis is very high, only 7 patients having recovered from among 62 pure cases reported in the literature.

Influenzal meningitis is more frequent and more fatal among infants and children than it is among adults. Of the 7 recovered cases, only 2 were infants less than 1 year old, though there have been 35 cases recorded in babies of that age. One of 5 recorded adult cases ended in recovery.

It has been pointed out in a previous paper[1] that the disease sometimes follows upon undoubted influenzal disease of the respiratory tract, and sometimes develops independently of obvious disease of that tract. Since the influenza bacillus is often present in the secretions of the respiratory mucous membrane in children suffering from a variety of diseases, during the wide prevalence of influenza, it is probable that the infection of the meninges is always secondary to respiratory infection and is accomplished chiefly through the blood current. Direct infection from the nose can not be excluded and should be considered as a possibility. The probability of an ascending infection of the meninges from the nasal mucosa is supported by the observation that, in monkeys, the influenza bacillus appears in the nasal mucus after being injected into the subdural space of the spinal canal by lumbar puncture. However, all or nearly all cases of spontaneous influenzal meningitis in human beings are examples of influenzal bacteremia, since the bacilli have been cultivated in large numbers, before and after death, from the heart's blood. The same general fact is true of experimental influenzal meningitis in the monkey. When the condition is produced by means of a subdural injection of a virulent culture, the bacilli can be cultivated during life and, at autopsy, from the heart's blood.

EXPERIMENTAL INFLUENZAL MENINGITIS.

We have succeeded in producing a condition of acute meningitis in monkeys that resembles, both clinically and pathologically, the spontaneous disease as it occurs in human beings. But only virulent

strains of *B. influenzæ* can be used to produce such an experimental meningitis, the virulence being tested upon white mice, guinea pigs, and rabbits. Influenza bacilli isolated from the respiratory organs during life or after death are, as a rule, virulent for mice and guinea pigs. Of 70 strains so tested, only 4 have been found to be devoid of all virulence. The case is quite different for the rabbit, since only four strains derived from the lungs showed virulence for these animals, and in the human patients from whom three of these strains were obtained, a blood invasion by the bacilli had taken place. The fourth strain was grown in pure culture at autopsy from a lung which showed the lesion of influenzal broncho-pneumonia, the blood remaining sterile. The significance of these facts will be discussed later. They are here used to contrast the virulence of the respiratory strains with that of the meningeal strains of influenza bacilli, bringing out the point that while all the meningeal strains except one (nine in number) tested upon young rabbits proved to be virulent, a few respiratory strains were found to be just as virulent for these animals. Furthermore, so far as our experiments went, it was found, in a general way, that bacilli that were virulent for rabbits also proved to be virulent for monkeys, and vice versa.

In the monkeys experimented on the effects of the subdural injection of an effective dose of a virulent influenza culture make themselves manifest in about five hours after inoculation. The first noticeable effect is a disinclination to move about actively, although the monkey may not show severe symptoms for 12 or even 24 hours. Death may result as early as 36 hours after the inoculation or it may be delayed for three or four days.

TREATMENT WITH ANTI-INFLUENZAL IMMUNE SERUM.

Having produced influenzal meningitis in monkeys, the next step was the attempt to treat it. For this purpose an anti-influenzal serum from a goat, immunized by means of the injection of virulent strains of influenza bacilli during a period of 18 months, was available. Injections of this immune serum, made at intervals varying from 1 to 24 hours after the introduction of the bacilli into the subdural space, cured monkeys after very severe illness.

The serum is not bacteriolytic in its action, but its opsonic content is very high. As a result of the serum injection the influenza bacilli in the cerebrospinal fluid are more freely phagocyted, their number is reduced, their capacity of growth is diminished, and the eruption into the blood is arrested. Along with these effects go cessation of the local inflammatory process and progressive improvement in the clinical symptoms, usually followed by rapid restoration to health.

HUMAN CASES TREATED.

Three human cases of influenzal meningitis have been treated with the anti-influenzal serum.[2] The first was an infant 3 months old, a patient at the Nursery and Child's Hospital, who developed symptoms of meningitis after an attack of rhinitis, bronchitis, and otitis which had persisted for several weeks. On the third day of the attack of meningitis 8 cubic centimeters of anti-influenzal serum was injected into the spinal canal. In the next 24 hours there was a fall in temperature and an improvement in the general condition. The following morning 15 cubic centimeters of the serum were injected, and within 15 minutes the baby collapsed and died in spite of heroic attempts at stimulation. While care had been taken to inject a smaller amount of fluid than had been withdrawn, the effect on the blood pressure of so young a child was evidently more serious than was indicated by the pulse and respiration. Had Sophian's method of watching the blood pressure been employed in this case, the collapse would probably not have occurred. Pure cultures of *B. influenzæ* were grown from the cerebrospinal fluid and from the pus of the middle ear, while the bacilli were also present in the nose and throat.

The second case came under the observation of Dr. C. H. Dunn, of Boston. A girl of 4 years had had symptoms of irritability and headache for two weeks before convulsive twitchings began. Two days later, the diagnosis having been established bacteriologically, anti-influenzal serum was injected, and the dose of 30 cubic centimeters was repeated three times. At first an improvement in the pulse and temperature was noted, but death occurred on the seventh day. While the cerebrospinal fluid had become more cloudy as the disease progressed, phagocytosis became marked after administration of the serum. *B. influenzæ* was grown in pure culture from the cerebrospinal fluid before death and from the meningeal exudate and heart's blood at autopsy.

The third case was that of a boy 13 months old, admitted to the Babies' Hospital on the third day of his meningitis, which followed an attack of pneumonia. After two injections of the anti-influenzal serum the temperature, pulse, and general condition were greatly improved, and the serum was omitted for a day. Then a rise of temperature occurred, convulsions became severe, and death ensued on the sixth day. At the autopsy an extensive lepto-meningitis and purulent ependymitis were found. *B. influenzæ* was cultivated from the cerebrospinal fluid during life and from the meninges, heart's blood, and lung after death.

These results are not entirely discouraging. In all three patients decided improvement followed the administration of the first dose of

the anti-influenzal serum, which, we believe, was not strong enough for use in the small doses which must of necessity be given to young children if untoward effects are to be avoided (as in case 1). A horse has now been immunized for about a year and its serum gives a higher opsonic index than was ever obtained with the serum of the goat. We are encouraged to hope that the anti-influenzal horse serum will yet prove effective in curing human cases of influenzal meningitis.

CHARACTER OF THE BACILLI ISOLATED FROM CASES OF INFLUENZAL MENINGITIS.

It is necessary to say a word as to the relation of the bacillus isolated from our cases of influenzal meningitis with the so-called *Bacille méningite cérébro-spinale septicémique* of Cohen.[3]

Cohen insists that the two bacilli are not identical and that the disease is not influenzal meningitis, but cerebrospinal septicemic meningitis. He admits the morphological and cultural identity of the two organisms, but finds differences in their agglutinative, conglutinative, and protective powers and, above all, in their pathogenic effect upon laboratory animals. In my hands, serum reactions with *B. influenzæ* have been unsatisfactory as a means of differentiation of strains. That is, agglutination tests, opsonic tests, and protection tests with immune goat serum have given identical results, whether made with virulent meningitis strains or with a perfectly innocuous strain cultivated from the throat of a child with mild influenzal bronchitis.

As to the virulence of influenza bacilli, strains of *B. influenzæ* freshly isolated from the throat, nose, or bronchial secretion of patients suffering from influenza, with or without pneumonia were, with few exceptions (4 of 70), virulent for mice and guinea pigs, but not for rabbits. On the other hand, all but on strain isolated by us from the cerebrospinal fluid in cases of meningitis were virulent for rabbits, and Batten [4] reports a recovered case of influenzal meningitis in a child 14 months old, from whose cerebrospinal fluid he isolated a strain of *B. influenzæ* which proved to be entirely without virulence for mice, guinea pigs, and rabbits. No blood cultures are mentioned. In all our cases of influenzal meningitis the virulent bacilli were found in the heart's blood before or after death, or both. It is a well-known fact that it is rare to find *B. influenzæ* in the heart's blood in routine autopsy cultures, Wohlwill [5] having failed to find it among several hundred autopsies at the Eppendorfer Krankenhaus. At the Babies' Hospital during a period of four years, among 753 autopsies, it was encountered only eight times, five times in influenzal meningitis and three times in cases of influenzal pneu-

monia with normal cerebrospinal membranes. It is an interesting fact that these three respiratory strains were as virulent as any one of the meningeal strains and that they entered the general circulation, both in the human cases from which they were cultivated and in the animals inoculated in the laboratory. That the children did not live long enough to develop meningitis is possible. Had they done so the bacilli would be classified as *Bacilli meningite septicémique*, while at present we must regard them as virulent strains of *B. influenzæ*. That the influenza bacillus does invade the blood stream was admitted by Pfeiffer when he so identified the bacillus Slawyk[6] had isolated from the cerebrospinal fluid, blood and joint pus from a case of influenzal meningitis in 1899. A most interesting case in this connection was one of broncho-pneumonia, seen at the Babies' Hospital, in which the influenza bacillus was isolated in pure culture from the lung at autopsy while the heart's blood remained sterile. This strain of *B. influenzæ* was virulent for rabbits and guinea pigs, and proves that virulence may be an attribute of influenza bacilli found in the respiratory tract, whether or not such bacilli enter the general circulation. That such bacilli do enter the blood without causing seropurulent meningitis is shown by the other three cases cited, as well as by the following one: A boy 9 months old was admitted for lobar pneumonia, and a blood culture made with blood obtained from the external jugular vein on the fourth day of the disease proved to be negative, but on the ninth day both pneumococci and influenza bacilli were found in the child's blood. On the twelfth day the culture was again negative and the child made a perfect recovery without any symptoms of meningitis. The influenza bacillus isolated from his blood proved to be virulent for rabbits.

It should not be forgotten that tests for virulence, to be of value, must be made with the earliest generations of *B. influenzæ* immediately after isolation from a human lesion. Like other bacteria, this bacillus loses its virulence on artificial cultivation outside the body.

Instead of making a distinct separation of the bacillus of septicemic meningitis from the influenza bacillus, it would seem to be simpler, and in keeping with all the facts, to say that while the majority of influenzal infections of the respiratory tract are due to nonvirulent bacilli, such infections are occasionally due to virulent strains, and that a virulent respiratory infection may become a general one, with or without inflammation of the cerebrospinal meninges. Moreover, nonvirulent influenza bacilli have been cultivated from cases of cerebrospinal lepto-meningitis. The virulence referred to here is the power to kill young rabbits of about 1,000 grams weight within 24 hours after an intravenous inoculation of one blood agar slant culture of 24 hours' growth, suspended in 1 cubic

centimeter of salt solution, the influenza bacillus being recovered in pure culture from the heart's blood and organs of the animal.

SUMMARY.

Influenzal meningitis can be produced in monkeys by means of subdural injection of virulent influenza bacilli.

The experimental disease can be cured by means of subdural injections of anti-influenzal immune serum.

Three human cases treated with the serum showed temporary improvement, but none recovered.

From the fact that virulent influenza bacilli are sometimes found in lesions of the respiratory tract, whence they may enter the blood without causing meningitis, while virulent influenza bacilli are sometimes found in the cerebrospinal fluid in cases of meningitis, it would seem that a separation of *B. influenzæ* from *Bacille méningite cérébro-spinale septicémique* (Cohen), on the ground of virulence, is not possible.

[1] Wollstein, Journal of Exp. Med., 1911, xiv, 73.

[2] I am indebted to the house staff of the Nursery and Child's Hospital and of the Babies' Hospital and to Dr. C. H. Dunn, of Boston, for the history of these cases.

[3] Cohen, Annales de l'Inst. Pasteur, 1909, xxiii, 273.

[4] Batten, F. G. The Lancet, 1910, I, 1677.

[5] Wohlwill, Münch. med. Wochens., 1908, LV, 328.

[6] Slawyk, Zeits. f. Hyg., 1899, XXXII, 443.

PROTECTIVE INOCULATION.

EXPERIMENTAL AND CLINICAL STUDIES ON THE USE OF LEUCOCYTE EXTRACT IN THE TREATMENT OF ERYSIPELAS, PNEUMONIA, AND OTHER INFECTIONS.

PHILIP HANSON HISS, Jr., M. D., Professor of Bacteriology, College of Physicians and Surgeons, Columbia University, New York.

In the past most workers have, in their study of infection and their search for biological therapeutic agents, directed their energies to the production of specific antisera and have, with few exceptions, neglected to approach the question of the treatment of infections from the side of the intracellular resisting agents of the system. In many infections, however, the ultimate weapons of defense of the system are the leucocytes, either in their normal state, acting as phagocytes, or possibly when breaking down in the circulation or in exudates.

It seemed to me therefore probable that we have certain diseases, not especially amenable to serum treatment, in which the ultimate immunity or defense is largely cellular, not only in the sense of phagocytosis and digestion, but in the neutralization or destruction of poisons which are formed by the bacteria or arise from the disintegration of the bacteria and their products—a mechanism in which the protecting cells or their products after their disintegration must intervene and, largely unaided by antitoxic bodies in the plasma, neutralize the poisonous products of the invading microorganisms.

It was this thought that suggested to me the idea of treating disease by aiding the leucocytes by furnishing them as directly as possible with the weapons which were being taken away from them in their fight with invading microorganisms, and to protect them thus from destruction and give them an opportunity to recuperate and carry on successfully their struggle against the invading germs. These weapons, whatever might be their nature, I assumed might possibly be furnished by an extract of the active substances of the leucocytes themselves—substances not ordinarily given up to the plasma or serum—and I also assumed that extracts would be more efficacious than living leucocytes themselves, introduced into the infected animal, since, if diffusible, they would be distributed impartially to all parts of the body by the circulatory mechanism and, as quickly as absorption would permit, relieve the fatigued leucocytes and protect, by any toxin-neutralizing or other power they might possess, the cells of highly specialized functions.

This idea of immunity differs from one that simply assumes the cells as the source of all immune bodies, in that it takes into consideration the presence and production in the leucocytes of agents which are not normally given up to the plasma, but which are able to reproduce themselves and carry on the functions of coagulation, of digestion, or of neutralization simply for the benefit and protection of the individual cell, while not being secreted or excreted by the cells for the more general benefit of the cell community at large.

It seemed to me that when these sources of protection are overtaxed or fail to act efficiently, the most reasonable course is, if possible, to support the system by introducing into the infected animal or man the substances composing the chief cells or all the cells of an exudate from normal or immunized animals in the most available and diffusible form, as little changed by manipulation as possible.[1]

Most other workers on this subject have been chiefly interested, apparently, in elucidating the direct germicidal action of certain leucocyte extracts on bacteria, and in bringing out differences between the serum bactericidal bodies and the bactericidal bodies of the leucocytes—in other words, with the mechanism of the bactericidal activities of leucocytes as shown *in vitro* and in the peritoneal cavity.

Attempts to influence infection by the use of organ extracts have also been made, apparently with little success. The thought, however, underlying most of this work differs from my own, as these experimenters have adopted such a course, arguing that certain organs may be the source of true antitoxins, or of the so-called immune bodies—amboceptors—and simply contain them in greater quantity than does the serum.

My work, on the other hand, as I have endeavored to make clear, has been based on another conception, and has had, as its immediate object, the practical determination of the curative effects of such extracts. These experiments and their practical applications have now extended over five and a half years.

THE TREATMENT OF INFECTION IN ANIMALS WITH LEUCOCYTE EXTRACT.

Passing now from these questions of theory, I will outline briefly the result of the treatment of infections in animals with leucocyte extracts. These infections or poisonings have usually been brought about by intravenous inoculations and, as a rule, the treatments with extract have been given subcutaneously, although at times intraperitoneally.

The infections to which I wish to call attention chiefly in the experiments on animals are staphylococcus, streptococcus, pneumococcus, typhoid, dysentery, meningococcus, and cholera.

Staphylococcus infections in animals.[3]—If we analyze our series of staphylococcus infections, we find that animals receiving subcutaneous injections of rapidly fatal doses of *Staphylococcus pyogenes aureus* can generally be saved by treatment with the extract of normal leucocytes of rabbits, even in small doses, especially when these are given intraperitoneally. When intravenous injections of staphylococcus are practiced, the results are different, but treated animals usually survive the controls many days, and present modified histologic pictures.

Streptococcus infections in animals.—In experiments with streptococcus infections I have worked only with those brought about by intravenous injections. In these experiments we find a marked lengthening of life and even a survival of the treated animals, and better results in the animals treated early than in those treated late. All of the animals which lived long enough developed articular or periarticular lesions, which tend to distinguish these infections from pneumococcus infections, which, as we shall see, seldom or never give rise in rabbits to such localizations.

Pneumococcus infections in animals.—If, in my series of experiments on pneumococcus infections, we consider the animals treated with the extract of leucocytes of normal rabbits, we find that in such

animals an infection, surely fatal in untreated rabbits, becomes significantly modified in treated animals, even if this treatment be delayed many hours. Thus, out of 8 control animals used in four experiments in which the intravenous infecting dose was the same, all died, averaging only 45 hours of life after being infected. Of the animals treated—some as late as 24 hours after infection—9 out of 12, or 75 per cent, survived the infection, three died with an average life of 60 hours after infection, two of them not having received treatment until the expiration of 24 hours.

These are not selected examples, but are records of events as they developed in our regular research tests, and have been fully confirmed by experiments undertaken in elucidation of other points, and are unmistakably indicative of the powerful beneficent action of such extracts on pneumococcus septicemia in rabbits.

On the other hand, living leucocytes, introduced subcutaneously, or even peritoneally, have little or no effect on systemic infections.

Typhoid infections in animals.—We find that typhoid infections, if indeed we may really call them such, in rabbits are essentially different from those caused by such organisms as staphylococci, streptococci, and pneumococci. The animals seem rather to suffer an acute intoxication, from which they either die within a very limited time, when organisms may be recovered from them, or recover completely, or go into a state of cachexia, but without organisms in the blood or organs. In my experiments the animals, as is usual after toxic doses of typhoid bacilli, showed signs of poisoning, remaining quiet and refusing all food for some hours. The animals receiving protection with leucocyte extract, shortly after this treatment, usually seemed worse than the control, and to the inexperienced would appear the most likely to die. This might possibly be due to a more rapid liberation of toxic substances by enhanced bacteriolytic processes, either brought about by a fuller complementing of immune bodies by the extract, or by special digestive bodies of the leucocytic extract, or it might be due to a somnolent state following a relief from active poisoning. That the poisoning in reality was fundamentally less severe than in the more normal-appearing control is, however, shown by the return of the treated animals to normal condition and weight, the weights following a perfectly logical order—untreated animal, animal treated late, animal treated early, as is illustrated by the following examples: A rabbit of 1,125 grams weight received a large but not immediately fatal dose of typhoid bacilli intravenously on April 8, which dose was repeated on April 15 and 22, the animal dying on April 29, weighing 895 grams; while another rabbit, weighing 1,108 grams, received the same amount of typhoid bacilli, but treated with leucocyte extract within five hours after the infect-

ing dose, lost no weight and recovered; and a 1,104-gram rabbit, treated each time within one hour, actually gained 200 grams.

In this experiment no organisms were alive in the control, so that the animal died from poisoning and interference probably with metabolism and excretion due to cellular changes.

In another experiment the dose of typhoid bacilli was so toxic that the temperature fell immediately instead of rising. The effect of the extract in the early-treated animal was not a further lowering of the temperature, but an arrest and more abrupt rise than in the control and the animal treated after five hours. Furthermore both the control and the later treated animal had bad diarrhea within two hours, but the animal treated in one hour did not have diarrhea.

Such experiments with leucocyte extracts on typhoid infections in rabbits are sufficient for illustration, and the conclusion from them seems unavoidable that leucocyte extracts have a remarkably beneficial modifying action on the course of typhoid infections or poisonings in rabbits.

The same holds true in infections in guinea pigs treated with rabbit leucocyte extracts, but, apart from noting the fact here that subcutaneous injections, used curatively, are active in guinea pigs, it does not seem of import to detail such experiments at this time.

Meningococcus infection in animals.—In meningococcus experiments rabbits suffer marked intoxication, if not, indeed, in some instances a true infection, when given sufficient quantities of almost any race of meningococcus intravenously. During the epidemic of cerebrospinal meningitis occurring in New York several years ago I proved this to my satisfaction many times, so that for the purpose of the following experiments I had no hesitation in selecting rabbits as the test animal.

If we analyze briefly the results of our experiments on rabbits infected with meningococcus, we find the following: In every experiment the controls died.

The total number of control animals used in the experiments, in which the treated animals received normal leucocyte or immune leucocyte extract, was eight. These eight controls, averaging 1,254 grams, died with an average life of 20 hours after infection.

Of the treated animals there were 13; 9 of these recovered, and 4 died, over 70 per cent of recoveries.

The average weight of the 9 animals which recovered was 1,200 grams, and of the 4 which died 1,062 grams, 200 grams lighter than the controls, with an average life after the infection of 5.7 days.

The majority of the animals did not receive treatment until the expiration of 5 hours after inoculation, and a number of them not until 21 to 24 hours, some of the controls having at times died before

these animals were treated with leucocyte extract. Severer tests could hardly be devised, and when the results of such tests are compared with those attained with the use of serum they point strongly to the value of leucocyte extract in the treatment of this infection.

Cholera and dysentery infections in animals.—Experiments with cholera infection of guinea pigs and rabbits, and with infections due to either type of the dysentery bacilli in rabbits, which always proved fatal in the control animals, have shown that these infections yield to treatment with leucocyte extract in much the same manner as do the infections to which I have already called attention.

SUMMARY AND CONCLUSIONS FROM ANIMAL EXPERIMENTS.

The character of the exact action of the extracted substance in these various infections is, of course, at present largely a matter of conjecture.

The fact that treated animals, in some instances, appear more intoxicated than the untreated may indicate an enhanced lytic action and liberation of toxic substances from the bacteria, thus suggesting the presence in the extract of complementing bodies, or of digestive bodies peculiar to the leucocytes. Such bodies are, of course, known to be present and may play an active part, but the strongest impression given to one carefully following the experiments and noting the immediate effect on temperature and the conservation and quick return to normal weight of the treated animals is that the principal substance at work is one active in neutralizing poisons or preventing their formation, and thus able to relieve the animal economy and give the phagocytes an opportunity to carry on their work of ingesting the microorganisms and their nonsoluble products, thus permanently rendering them harmless.

The points which to my mind at present speak most strongly for the explanation of the beneficial action of leucocyte extracts, as either poison neutralizing or poison prohibiting, rather than primarily bactericidal or bacteriolytic, or even one of immediate phagocytosis, are, first, the effect on temperature; for, when the temperature is high, it tends to be lowered, and, when it is falling below normal from the intensity of the poisoning, it tends to rise on treatment, which is a sign, of course, under this condition, of returning strength on the part of an animal; and, secondly, the effect in preventing diarrhea, which is a sympton of poisoning in such intoxications. Animals treated in time rarely show diarrheal symptoms. Now, if the action of the extract were a poison-liberating one, we might possibly have a falling temperature when it is high, following the introduction of extract, caused by a further poisoning, but we should not have a rise in temperature in an already fatally intoxi-

cated animal; in the same way, if poison were liberated, animals receiving treatment should evince symptoms of diarrhea before the untreated ones. And, further, the experiments performed by Zinsser and myself *in vitro*, and in the peritoneal cavities of guinea pigs, strongly favor a toxin-neutralizing or coagulating action; for we were able to show, in a fairly satisfactory manner, that bacterial extracts were precipitated by leucocyte extracts, and we were unable to determine any marked extracellular intraperitoneal destruction even of such sensitive organisms as cholera vibrios, or, in fact, any immediate increase in phagocytosis; and yet the animals were better off than the controls. That the action is one affecting the poisons immediately, no matter what the effect on the bacterial cells may be, seems an unavoidable conclusion, since falls of temperature of several degrees may occur within a half hour to an hour after subcutaneous adminstration of leucocyte extract. This fact also practically rules out an explanation of the extract as being simply a stimulator of general leucocytosis from the leucocyte-forming bases of the animal; for, even if such a leucocytosis could occur in so short a time, we know from experiment that freshly obtained living leucocytes, when introduced into an infected animal, even intraperitoneally, are practically without effect on systemic infections. The lives of the animals are not lengthened and these intact leucocytes seem to have no influence on the temperature.

Intravenous injections of living leucocytes have not been tried, since the results of such a procedure are of purely academic interest, being entirely outside the realm of possibility in the treatment of human infections. The use of living leucocytes in the treatment of local infections is, of course, possible, but of limited application, both theoretically and practically, and their beneficial action would probably be due to the simple regeneration of the phagocyte army, or to extracts which, unsuspectedly, accompanied the supposedly intact leucocytes introduced.

THE TREATMENT OF INFECTIONS IN MAN WITH LEUCOCYTE EXTRACT.

The infections in man which I and my coworkers have treated, through the courtesy and request of various physicians, have been those due to the meningococcus, pneumococcus, streptococcus, staphylococcus, and colon bacillus.

There is not time, nor is this the place, to go into the histories of the individual cases. In connection with Dr. Zinsser in 1908 I published the results obtained in the treatment of a number of epidemic meningitis patients, and in a small number of patients suffering from lobar pneumonia and pneumococcus infections, and to these articles I must refer anyone interested for details of these earlier tests.[2]

Meningococcus cases.—It may be of interest to state, however, that 15 of the meningitis patients treated by us were under 15 years of age; of these, 3 died, leaving 80 per cent of recoveries with no sequelæ. Of the patients over 15 years, there were 7, of whom 5 died. This result may have been due to the fact that several of these adult patients were *in extremis* when admitted to the hospital. In spite of this, under treatment some of the patients showed a marked improvement, and did not die before 27, 7, 38, 11, and 25 days after treatment was begun. Of the children who were treated, but who died, 1 survived 79 days, 1, 62 days, and 1, a baby of 7 months, 12 days, after treatment was instituted.

It seems also of interest to note the fact that, in 7 cases in which treatment was begun subsequent to the seventh day of the disease, there was 100 per cent of recoveries without sequelæ. Treatment was not begun in these cases until the elapse of 17, 20, 47, 41, 53, 39, and 82 days after the first symptoms developed, and a reference to the histories would show that these patients were, as a rule, in grave condition.

Almost without exception there was an improvement in those symptoms which, in this disease, depend largely on the central nervous systems. Vomiting, delirium, stupor, and hypesthesia were usually diminished or entirely allayed after one or two administrations of quantities ranging from 5 to 20 cubic centimeters.

Marked reduction in the temperature following injections was noticeable in many of the cases. In some of these cases, however, the diminution of the fever was a temporary phenomenon, limited to the 24 or 48 hours immediately following the injection, a fact which also argues strongly for the idea of poison neutralization.

The actual percentage of recoveries among these patients was about 64 per cent. If 70 or 75 per cent be accepted as the usual death rate, and the basis for determining the value of the serum treatment of meningitis, then the fact that 64 per cent of our patients recovered would seem to indicate some curative value in the extract. And if this is true, it also indicates that if the antimeningitis sera are really toxin neutralizing, or contain the same antibodies as the leucocyte extract, then these sera should be efficacious when administered subcutaneously, which is not the fact. I am inclined to believe that a combination of these treatments, immune serum given subdurally and leucocyte extract subcutaneously, might lead to more favorable results than the use of either separately.

Lobar pneumonia.—The total number of lobar pneumonia cases treated by us personally with leucocyte extract of which we have satisfactory records are 53. Out of this number 3 ended fatally, a mortality of 5.6 per cent. Two of the fatal infections were in alcoholic patients. While this is of course not such an extended series as might

be desired upon which to base definite conclusions of the efficiency of the treatment, nevertheless the low mortality shown is encouraging, especially as the majority of the cases were severe, our aid not being asked until the patient was in an exceedingly unsatisfactory state. To those observing the course of the disease under this treatment, the most obvious effects of the extract were an almost immediate improvement in the feeling of well being of the patient, while, in the objective symptoms, the improved quality of the circulation and reduction of pulse rate, with a disappearance of cyanosis, usually accompanied by an immediate drop in temperature, were noted; some cases ending by an abrupt and early crisis, others coming to normal by a more gradual lysis. The spreading of the lesion was usually halted, and convalescence was usually rapid and uninterrupted. A striking effect of the treatment is the early disappearance of the distressing cough, which improvement has been especially apparent to the patients themselves. As to the blood pictures, it has been noticed that in patients growing progressively worse with a falling leucocytosis, that the leucocytes increased almost immediately, giving in a few hours a more normal and favorable blood picture. A general conclusion from a study of all our cases is that the disease is rendered largely benign, and in patients treated early, the length of the disease is markedly shortened. In cases treated late, the crisis usually comes on in a few hours.

The doses usually given have been from 20 to 60 cubic centimeters, and repeated every four hours until marked improvement occurs.

Such occurrences as these, backed by the conclusive evidence of the animal experiments, would certainly seem to warrant an extended and careful study of the influence of this agent on pneumococcus infections in man, and make us hopeful that many an otherwise fatal illness may become comparatively benign under its influence. This hope is strengthened by evidence gathered from the study of infection due to the streptococcus, so closely related to the pneumococcus in many ways.

Streptococcus infections.—Erysipelas is a streptococcus infection which is an ideal infection to study, as the chief lesion is in plain view, and there is usually a sharp temperature reaction in the infection. Moreover, a well-marked train of symptoms, which are undoubtedly toxic in origin, is generally present, and as the leucocyte extract seems to act primarily, at least in combating toxemia, we have therefore a comparatively reliable means at our disposal of judging of its effects, both on the lesion and systemic symptoms.

The mortality rate of erysipelas is given as about 10 per cent in adults; in children, as 75 per cent; and in infants under 1 year as almost 100 per cent. Erysipelas, therefore, can not be counted as a light infection.

Nevertheless, the opinion does not seem to be rare that erysipelas is a trivial, self-limiting disease that can safely be left to run its course under local treatment.

During the last two years, however, we ourselves have had reports of 12 fatal cases of erysipelas occurring not in patients of the extremes of age but for the most part in strong healthy adults. The need for more efficient therapeutic measures is therefore evident.

The series of erysipelas infections treated with the leucocyte extract comprises 126 cases of all types and grades of severity. The majority of infections were secondary to operative measures and might be classed as surgical erysipelas, while the others were of the so-called idiopathic form, as the origin could not be traced to any contributing trauma or known lesion. As regards severity, they were nearly all severe infections, and the great majority of them were of the most severe type that occurs. This was due to the fact that we were usually not consulted until the ordinary remedies had been tried, by which time the infection was well established and the systemic symptoms marked. Thus, with the exception of a few, the lesion had been present for a time, varying from several days to two weeks. Such cases, therefore, probably offer as fair a test of the value of a therapeutic agent as could be desired.

The results obtained have been so uniformly beneficial, constant, and marked that judging from them it would seem that in this disease we can almost prognosticate the results following the use of leucocyte extract.

In every case there was a marked reaction following its use, which in most cases was shown by a fall in temperature and a rapid improvement in the general condition.

In an average case of erysipelas, one of moderate severity, the constitutional symptoms, due to the absorption of the toxins, are well marked—headache, nausea, vomiting, delirium, sometimes active but usually of a low muttering type, and a sense of extreme depression. The local subjective symptoms are also marked and are very annoying, the heat, burning, and itching. In practically all the cases the symptoms disappeared within a few hours following the first injection of the extract; the headache, nausea, and vomiting disappeared, the mind became perfectly clear, and from a low, depressed, apprehensive state the patient passed into a state of comparative comfort, free from anxiety. The effect on the temperature varied with the class of patient and with the time that had elapsed between the onset of the lesions and the beginning of the treatment—in those treated early, within 24 or 48 hours of the onset, there was a sharp fall in the temperature curve, and the disease ended practically by crisis, the accompanying symptoms disappeared, and the rash ceased to spread.

In the cases treated later in the course of the disease there was usually not such a marked effect on the temperature, but the change in the general condition was just as marked and the course of the disease cut short. Locally, in all cases, whether treated early or late, the burning and aching pain disappeared in a few hours. Subjectively the patient was soon in an entirely different state.

As regards the effect of the extract on the local lesions, there was generally some further spreading, but the character of the lesion changed. The bright vivid crimson rash, usually seen in an otherwise healthy patient, soon ceased to spread and faded. The dull purplish rash, seen in the deeper erysipelas infections or in the asthenic type of patient, soon gave way to the bright crimson form, which change we take to be evidence of increased resistance, and this in turn faded away gradually. In the latter class of patients, where a severe infection was present with the corresponding systemic symptoms and a low temperature curve, a moderate rise of temperature at times occurred after the infection. This we looked upon as a favorable sign and as an evidence of increased resistance.

The duration of an average case of erysipelas, under the routine measures of treatment, is about 10 to 14 days. In our series of cases the average duration, whether treatment with the extract was instituted early or late, was 3–1 days after treatment was begun.

In practically all cases following the use of the leucocyte extract, had it not been for the mere physical presence of the diseased focus, the patient would have been considered well.

The extract took the place of all stimulation, and patients suffering from the most severe infections have been kept entirely comfortable by the use of the extract alone, with a pulse rate usually not rising above 90, thus showing the saving of the human economy.

With post-operative or surgical erysipelas one point is worthy of special notice. Most of these infections were complications of operations on the eye, ear, nose, and throat. The point to be noted is that under this treatment the healing instead of being delayed, as usual, was hastened and was complete in a much shorter time than in an uncomplicated case. We refer especially to mastoid wounds. This is directly contrary to the usual experience with such wounds, as very often, following erysipelas, it is necessary to do a second operation to clean out the flabby unhealthy granulations. The same would hold true with operative measures on other parts of the body.

The foregoing general description of the effects of leucocyte extract on erysipelas represents not only our own conclusions from the observation of patients so treated but is based largely upon conclusions drawn by the physicians and surgeons under whose care many of these patients were.

For purposes of analysis little would be gained by giving histories of the patients treated. The histories fall into more or less distinct groups which we simply summarize in the following table:

Statistical analysis of erysipelas cases.

Age of patient.	No. of cases.	Time of treatment.[1]		Average duration of treatment.	Termination of cases.	
					Recovery.	Death.
				Days.		
Infants (up to 1 year)	12	Early	5	4	3	2
		Late	7	6	5	2
Children (1 to 15 years)	10	Early	3	1.5	3	.....
		Late	7	3	7	.....
Adults (15 to 50 years)	94	Early	36	2.26	36	.....
		Late	58	3.5	58	.....
Over 50 years	10	Early	4	1.5	4	1
		Late	6	3.7	5	.....
Total	126	Early	48	2.3	46	2
		Late	78	4.05	75	3

[1] Early—Treatment begun within 3 days of appearance of lesion; Late—Treatment begun later than 3 days after appearance of lesion.

Recapitulation.

Total number of cases treated, 126; recovered 121, mortality 3.96 per cent.
General average duration of treatment, 3.18 days.
Number of recoveries under 1 year old, 8 out of 12.
Per cent of recoveries under 1 year old, 66.6 per cent.
General mortality rate, 3.96 per cent (all cases).
Mortality among patients over 1 year, 0.87 per cent; recoveries, 99.13 per cent.

In addition to these cases, Dr. Adrian Lambert, in his wards at Bellevue Hospital, has treated about 50 cases of erysipelas by this method, with extract supplied by us. While the history of these cases will be published in detail by Dr. Lambert, his conclusions are as follows:

Leucocyte extract will abort infections which are treated within the first 48 hours.

It will ameliorate the course of older infections and may abruptly terminate them; the longer the infection has existed, the less likely is the latter to take place, but it tends to shorten the course of the disease.

The toxic symptoms—delirium, headache, nausea, and vomiting—are modified and relieved; local pain is lessened.

The rash does not disappear immediately, but is apt to be localized.

The spreading intractable lesions of the back and body are apparently affected as readily as those occurring on the face and head.

Pus formation is aborted, and sequelæ are rare, if they occur at all. About 50 per cent of babies under 1 year of age have recovered from the erysipelas.

Our conclusions, as has been stated, are practically the same as these, although we show even a more favorable outcome of the treatment in babies under 1 year of age.

Staphylococcus infections.—Local acute and chronic staphylococcus infections respond almost immediately to treatment with the extract,

and furunculosis of intractable type is halted and apparently cured. Dr. Zinsser has treated 11 patients who had staphylococcus infection. In these, after treatment was begun, surgical interference was always unnecessary, and Dr. Dwyer has also treated a large number of patients with various staphylococcus infections with uniformly favorable results.

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[1] The method of obtaining these substances as used in animal experiments and the treatment of human subjects is at present as follows: Rabbits, of 1,500 grams weight or heavier, receive intrapleural injections of aleuronat. This is prepared by making a 3 per cent solution of starch in meat-extract broth, without heating, and adding to this, after the starch has gone into thorough emulsion, 5 per cent of powdered aleuronat. This is thoroughly mixed, boiled for five minutes, and filled into sterile potato tubes, 20 cubic centimeters into each tube. Final sterilization is done, preferably in an autoclave. The rabbit injections are carried out by injecting 10 cubic centimeters into each pleural cavity in the intercostal spaces at the level of the end of the sternum, in the anterior axillary line, great care being exerted to avoid puncturing the lungs. The rabbits are left for 24 hours, at the end of which time a copious and very cellular exudate will have accumulated in the pleural cavities. After killing the animals, this is removed by opening the anterior chest wall under rigid precautions of sterility, and pipetting the exudate into sterile centrifuge tubes. Immediate centrifugalization, before clotting can take place, then permits the decanting of the supernatant fluid. To the leucocytic sediment is then added about 2 cubic centimeters of sterile distilled water, and the emulsion is thoroughly beaten up with a stiff bent spatula. Smears are now made on slides, stained by Jenner's blood stain, and examined for possible bacterial contamination. It is well also to take cultures. Sterile distilled water is then added to each tube, about 10 volumes to 1 volume of sediment, and the tubes are set away in the incubator for seven or eight hours. At the end of this time the sterility is again controlled as above, and further extraction in the refrigerator continued until the extract is used. So far as at present determined, the preparation remains active indefinitely. Before use the preparation is thoroughly shaken to disseminate the sediment, which is then drawn into the syringe and injected subcutaneously along with the fluid into the animal or human.

[2] Journ. Med. Research, 1908, XIX, 323. See this article for details of the method and the following experiments on animals.

[3] Journ. Med. Research, 1908, xvi.

DISCUSSION.

DR. [illegible] LINEHAN, New York: In cases of furunculosis I have seen [illegible] from the use of the leucocyte extract than from that of [illegible]. I would like to ask Dr. Hiss whether he has seen any [illegible] injections, and how often. I observed in one case an [illegible] with temperature elevation after the fourth injection, [illegible] given within a few days after the first. The [illegible] subsided.

THE PRODUCTION OF ANTIRABIC IMMUNITY BY INTRASPINAL INJECTIONS OF VIRUS.

Dr. D. L. HARRIS, Bacteriologist to Hospital Department, St. Louis, Mo.

The object of this paper is to present the results of an attempt to produce a rapid antirabic immunity by direct immunization of the brain cells.

The method devised by Pasteur for the prevention of hydrophobia limited this work to large and well-equipped laboratories and required the patient to undergo treatment for a period of three weeks or more. Several modifications have been adopted from time to time, which have made the work of preparing the material less onerous and the treatment more available to the public, especially to those patients living at a distance from such a laboratory. In all antirabic institutes, whatever modification may have been adopted in the preparation of the material, the treatment consists in a number of injections into the abdominal wall. The result of this is an indirect immunization of the brain cells against the infective agent. In spite of all treatment, however, a small number of the patients die before immunity can be established.

During the past year I have described a method for preserving the virus used in antirabic immunization. This, in brief, consists in freezing with carbon dioxide snow the brain and cord of a rabbit infected with the disease and drying these in a vacuum at a temperature of —10° C. Material prepared in this manner, and kept free from moisture in an ice box (10° C.) loses its infectivity so slowly that after a preservation of 40 weeks one-tenth of a milligram, when injected subdurally, will produce paresis in a rabbit in 7 days; in other words, after 8 months of desiccation, its infectivity is equal to that of Pasteur's 2-day cord.

In testing the desiccated material from time to time to determine the effect of time, temperature, and light on the rate of loss of infectivity, I observed that some rabbits which had received subdurally a quantity of the virus slightly less than the minimal infective dose developed an appreciable and determinable immunity against subsequent subdural inoculations.

Ten rabbits were immunized in this manner, and the degree of immunity thus acquired was ascertained by one or more later tests. Of these ten, six resisted an injection sufficient to kill untreated controls. One did not develop the disease after an injection of twice the minimal infective dose. One survived the injection of 100 minimal infective doses. Two died on the fifteenth and seventeenth days, respectively, after the injection of twice the minimal infective dose.

Of seven rabbits that survived the first test, four were inoculated later with 10 minimal infective doses of street virus. Two survived

and two died on the eighteenth day. Table No. 1[1] gives the results of these experiments in detail. All injections were made under the dura after trephining.

Tests made in one lot of material which had been kept for some months at room temperature in daylight showed this to be noninfective, and it was observed that the rabbit inoculated with this material had also acquired an immunity. (Table I. R. No. 9.)

Following this a number of rabbits were given larger quantities of noninfective material intraspinally.

In these experiments, the details of which will be seen in Table No. 2,[2] rabbits 1, 2, and 3 were injected intraspinally with material which had been kept in an ice box for 66 days, and then in the light at room temperature for 219 days. Rabbits 4, 5, and 6 were injected with material that had been kept in a north window, room temperature, for 11 months. When these six were injected the technic of making the spinal puncture was undeveloped, and it was suspected at the time that the needle had not entered the spinal canal of rabbits Nos. 1 and 4. Their susceptibility to a later inoculation of four minimal infective doses showed this suspicion to have been well founded. Rabbits Nos. 7 to 19 were injected with material which had been in the dark at room temperature for eight months. Rabbits 20 to 23 were injected with material which had been kept in the presence of P_2O_5, which, it has been demonstrated, causes a relatively rapid destruction of virulence.

Rabbits No. 24 to 27 were injected with desiccated street virus whose infectivity had been destroyed by placing it in direct sunlight (west window) for three weeks. The material was obtained from a case of rabies in a woman and was the brain of a rabbit, first passage. It had been desiccated five months. It will be seen that three of these rabbits were not immune to 10 minimal infective doses 14 days after the injection, but that the fourth resisted a similar inoculation 28 days later. The action of direct sunlight may have been a factor in lessening the immunizing capacity of the material. It is of interest to note that street virus may be used for immunization by this method.

Rabbit No. 28 was injected subdurally (trephine) with material which had been kept in an ice box for 7 months, and in one of the laboratory rooms in daylight for 39 days. Rabbit No. 29 is the same as No. 7, and, after surviving this test, was reinoculated 44 days later.

These experiments show that the brain of a rabbit may be directly immunized by a single intraspinal injection of nonvirulent material to such a degree that two weeks later the animal successfully withstands a subdural injection of 10 to 20 times an otherwise fatal dose. The immunity is acquired so rapidly that the intraspinal injection

of 5 milligrams or more will protect against a simultaneous inoculation of a minimal infective dose injected subdurally (trephine).

Similar experiments were made on dogs, as follows: Three dogs were injected by lumbar puncture with 50 milligrams of noninfective material, and 16 days later were inoculated under the dura with $\frac{1}{10}$ milligram of the medulla of a rabid dog (desiccated).

In another series one dog was given 10 milligrams of a noninfective desiccated brain; two dogs 20 milligrams; two dogs 40 milligrams; and the five were inoculated eight days later with $\frac{1}{10}$ milligram of desiccated street virus. Two other dogs were injected with 50 and 25 milligrams intraspinally, and at the same time were inoculated under the dura with $\frac{1}{10}$ milligram of desiccated street virus. Two dogs were used as controls. The estimated amount of infective virus received by each of these 12 dogs was five times the infective dose for rabbits.

One of the control dogs developed furious rabies on the fourteenth day. The other control became emaciated 5 weeks later; on the forty-fourth day refused food, and died on the forty-sixth day after a paralysis which developed a few hours earlier. The autopsy did not reveal any cause of death and Negri bodies were not found in the brain. One of the two dogs, inoculated and immunized at the same time, became extremely emaciated 5 weeks later, developed paralysis on the thirty-sixth day, and died on the thirty-eighth day. The remainder of the immunized dogs have shown no recognizable injury following the inoculation.

The above experiments seem to show that it is comparatively easy to immunize rabbits against rabies by a single intraspinal injection of noninfective desiccated "virus," and that the resulting immunity is acquired with surprising rapidity. The test on the dogs is somewhat unsatisfactory, because the amount inoculated was too small to produce a definite and early outbreak of the disease in both control animals. It does appear, however, that the intraspinal injection is not followed by any ill results.

Whether or not fixed virus may be rendered noninfective by methods other than the one I have employed without at the same time lessening its immunizing value is a question which offers an opportunity for further investigation. It appears that the material whose infectivity was destroyed by P_2O_5, and by direct sunlight, did not have as great an immunizing value as the material which had been allowed to die more slowly.

If further investigations show that the intraspinal injections of this material are harmless to animals, and that immunity is regularly and rapidly conferred, we may be in possession of a means of saving some of those patients who have received severe injuries about the face and who now succumb in spite of the treatment em-

ployed at the present time. Another advantage of this method is that the immunizing property of the material I have used is not affected by age, and it may be stored in quantity and kept anywhere for immediate use.

[1] TABLE No. 1.

Rabbit.	Amount of first inoculation (in minimal infective doses).	Time of second inoculation.	Amount (in minimal infective doses.) F. V.	Time of third inoculation.	Amount (in minimal infective doses of street virus).	Result.
		Days.		*Days.*		
No. 1	$\frac{1}{2}$	30	2			Died fifteenth day.
No. 2	$\frac{1}{2}$	58	2			Died seventeenth day.
No. 3	$\frac{1}{2}$	29	2			Immune.
No. 4	$\frac{1}{2}$	43	1	72	10	Died.
No. 5	$\frac{1}{2}$	43	1	72	10	Do.
No. 6	$\frac{1}{2}$	27	1	78	10	Immune.
No. 7	$\frac{1}{2}$	27	1	107	10	Do.
No. 8	$\frac{1}{2}$	78	1	107	100	Died.
No. 9	$\frac{1}{10}$	27	1	107	200	Do.
No. 10	$\frac{1}{2}$	36	100	55	200	Do.

[1] Milligram.

[2] TABLE No. 2.

Rabbit.	Amount injected.	Time of inoculation.	Amount in minimal infective doses of fixed virus.	Result.
No. 1	20 milligrams of fixed virus	10 days later	4	Died.
No. 2	do	do	4	Immune.
No. 3	do	do	4	Do.
No. 4	do	do	4	Died.
No. 5	do	do	4	Immune.
No. 6	do	do	4	Do.
No. 7	25 milligrams of fixed virus	Same time	1	Do.
No. 8	20 milligrams of fixed virus	do	2	Do.
No. 9	5 milligrams of fixed virus	4 days later	5	Do.
No. 10	20 milligrams of fixed virus	do	10	Died.
No. 11	5 milligrams of fixed virus	6 days later	10	Do.
No. 12	10 milligrams of fixed virus	do	15	Immune.
No. 13	15 milligrams of fixed virus	do	10	Do.
No. 14	5 milligrams of fixed virus	8 days later	20	Died.
No. 15	10 milligrams of fixed virus	do	20	Do.
No. 16	do	do	30	Do.
No. 17	15 milligrams of fixed virus	do	20	Immune.
No. 18	20 milligrams of fixed virus	14 days later	20	Died.
No. 19	do	15 days later	10	Immune.
No. 20	20 milligrams of fixed virus (P_2O_5)	Same time	2	Died.
No. 21	do	14 days later	5	Immune.
No. 22	do	do	10	Died.
No. 23	do	do	20	Do.
No. 24	12 milligrams of street virus	Same time	4	Do.
No. 25	do	14 days later	10	Do.
No. 26	20 milligrams of street virus	do	20	Do.
No. 27	12 milligrams of street virus	28 days later	10	Immune.
No. 28	20 milligrams of fixed virus	11 days later	10	Do.
No. 29	25 milligrams of fixed virus	44 days later	10	Do.

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THE ETIOLOGY OF TRACHOMA.

ANNA W. WILLIAMS, Division of Laboratories; Director WM. H. PARK, Health Department, City of New York.

For the past two years the New York City Health Department has been studying trachoma and allied conditions and it plans to continue these studies for about two years more. The full report will contain details of the work. So far in our investigations we may summarize our results briefly under seven heads as follows:

I. Hemoglobinophilic bacilli are found in cases of "trachoma" practically coincidently with "Prowazek (trachoma) inclusions."

II. These bacilli show the same cycle of development as that of the "Prowazek inclusions."

III. These bacilli so far can not be differentiated from *B. of Koch-Weeks* or *B. influenzae.*

IV. Clinically, cases beginning as acute contagious conjunctivitis (Koch-Weeks infection) may pass into the condition known as trachoma.

V. The above facts lead to the hypothesis that "trachoma" is caused by infection with one or more of the group of hemoglobinophilic bacilli, producing primarily an acute inflammation, and, secondarily, in susceptible cases, a subacute and chronic productive inflammation.

VI. Acting on this hypothesis for the past year and a half the acute contagious conjunctivitis cases as well as those of "trachoma and allies" have been closely followed and treated in schools and homes. Now, there are practically no new cases of "typical trachoma."

VII. An opportunity to test further this hypothesis is afforded by the establishment of special mixed classes in schools for the isolation, study, and treatment of these cases.

There are just a few points which I wish to emphasize under each of these heads.

I.

1. *In all fresh untreated* cases of papillary trachoma, where the Prowazek (trachoma) inclusions were present, we found the hemoglobinophilic bacilli. In many cases which were old when first seen, and in a number of recovering cases we found neither the Prowazek inclusions nor the hemoglobinophilic bacillus. In the rest of these cases the inclusions and bacilli were irregularly present, the inclusions generally in small numbers.

2. *Frequency of isolation.*—Other investigators have isolated members of this group of bacilli from trachoma, but not so regularly.

Our success is probably due to our special technic. This technic has already been published.[1]

The bacilli often may not be isolated because they are so readily overgrown by other microorganisms, especially by the staphylococcus pyogenes, which, as you know, is found not seldom in inflammations of the conjunctiva.

We hoped to obtain some help in isolating our bacillus from these cases from Churchman's (1912) gentian-violet-medium but have been disappointed, because we found that while this medium inhibited the Gram positive organisms in pure cultures it did not appreciably inhibit them in mixed cultures with the blood medium used by us.

II.

Under head II we wish to emphasize the resemblance between our bacilli and the trachoma inclusions.

1. These bacilli in young cultures stain as the initial bodies of Lindner. Later they form tiny metachromatic granules, passing through a cycle similar to that described for the trachoma inclusions.

We have carried through a number of different varieties of bacteria found in diseased conjunctivæ, in order to find out whether other varieties show a similar cycle, and we have found that while most of them show a few metachromatic granules in later cultures, only one variety shows them to the extent seen in our hemoglobinophilic bacilli. It is interesting to note, considering Hertzog's hypothesis that the inclusions are altered gonococci, and considering the work done on the finding of trachoma inclusions in ophthalmia neonatorum and in vaginal and urethral cells, that the other variety is the gonococcus. We have found in certain cases of gonorrheal ophthalmia all stages of inclusions from gonococcal forms up to metachromatic granular forms, and we have found certain minute differences between this series of changes (corresponding with those found in pure cultures of the gonococci) and the series of changes seen in the inclusions of chronic conjunctivitis cases in which we have found the hemoglobinophilic bacilli, where again we find a complete series of changes in the inclusions, from definite bacillus forms up to metachromatic granular groups; these, also, as I have said, corresponding with the changes observed in pure cultures.

The chief differences so far observed in the cycle of these two species of bacteria is that, in the gonococcus, the groups are more dense and the metachromatic granules are finally smaller than in the hemoglobinophilic bacilli.

From these observations, it seems to me quite probable that the gonococci, as well as the hemoglobinophilic bacilli, produce so-called "Chalmydozoal, Prowazek, or Trachoma inclusions."

Of course, there may be cases of mixed infection. If these are facts, they explain all of the recent contradictory findings in gonorrhoeal, as well as in papillary, conjunctivitis (trachoma) cases. This hypothesis also explains Dr. Noguchi's (1911) findings in his series of gonorrhoeal ophthalmias showing the Prowazek inclusions.

In regard to the etiology of trachoma, however, we must still consider two important series of investigations—one, animal experiments, and the other filtration experiments.

A number of investigators have reported the production of trachoma in the conjunctiva of Pavian monkeys, after suitable inoculations. Unfortunately, we have had, so far, only a few Macacus species with which to work, and in one out of four we have gotten a moderate subacute conjunctivitis, without inclusions, after inoculations with our bacilli from which we recovered the bacillus.

In regard to filtration, it has been claimed that the virus of trachoma is filterable. The results of these investigations are still under discussion. I can only say that we are just starting experiments on the filterability of our small bacilli, especially with cultures at different stages, in order to determine the passage of the tiny granules; for, without doubt, as with other bacilli, some of these granules at a certain stage of their growth represent the last living element of the bacilli. With sufficient dilution and pressure they may with comparative ease pass at least some of the coarser filters.

III.

Under the third heading I wish to call attention to the following points:

1. Our bacilli with the influenza bacilli, as well as all of the many strains of Koch-Weeks bacilli with which we have worked, are so far, strict hemoglobinophiles in pure cultures.

Those observers who have obtained successive growth of the Koch-Weeks bacillus on serum, must have used serum which contained a small amount of hemoglobin. These bacilli will grow in serum containing 1:1000 blood, which means a quantity of hemoglobin that can not be detected by ordinary tests. The spectroscope does not discover this amount. We have found only Adler's benzidene test positive.

2. All the other tests we have used to differentiate these strains, such as complement deviation, simple and acid agglutination, etc., have, so far, shown no clear-cut differences between them. There is no doubt, however, reasoning from the findings in other similar bacterial groups, that there are, at least, distinct varieties among them, and that there are variations in pathogenicity which could account for the different clinical findings.

IV.

Under the fourth heading we consider the clinical study of our cases.

The relationship between acute contagious conjunctivitis and trachoma has often been discussed. But very few observers have had, or have taken the opportunity (judging from published reports) to follow cases beginning as acute contagious conjunctivities through a series of attacks until a subacute and chronic condition is reached with all of the earmarks of trachoma. We have, apparently, been able to do this in a certain number of cases, and obtained, apparently, good histories in a certain number of other cases, not only in New York City, but in the Kentucky Mountains where trachoma is in evidence. This has materially aided us in reaching our conclusion, that, clinically, cases of trachoma are intimately related to acute contagious conjunctivitis.

V, VI, AND VII.

Our hypothesis in regard to the etiology of trachoma, which is given under the fifth heading, requires much study before it can be proved; but, considering the results stated in the sixth heading, practically, we are justified in using it as a working hypothesis. And, in the immediate future, with the establishment of the special mixed classes the Board of Education has allowed us, we hope that while we are attempting to cure and stamp out the disease, we may at the same time add material to the evidence as to the nature of trachoma, at least in our New York City school children.

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[1] Significance of the group of hemophilic bacilli in conjunctivitis, especially in that of trachoma. Proceedings of N. Y. Path. soc. an. 10–1912; New York Med. J., Mar. 16, 1912.

DISCUSSION.

K. LANDSTEINER fragt an, ob irgend ein Unterschied zwischen den von Williams beobachteten Bacillen und dem von Müller als Ursache des Trachoms vermutheten haemoglobinophilen Bacillus besteht.

WEDNESDAY MORNING, SEPTEMBER 25, 1912.

PARATYPHUS UND PARATYPHUS-ÄHNLICHE BAKTERIEN MIT BESONDERER BERÜCKSICHTIGUNG IHRER VERBREITUNG IN DER AUSSENWELT UND IHRER BEZIEHUNGEN ZU MENSCH UND TIER.

A. Weber, Dr. med., Geh. Reg. Rat, Direktor der bakteriologischen Abteilung des Kaiserlichen Gesundheitsamtes, Berlin.

Auf dem XIV. Internationalen Kongress für Hygiene und Demographie, Berlin 1907, erstatteten *Babes* und *Löffler* Referate über die Bazillen der Typhusgruppe, in denen sie den dankenswerten Versuch machten, die grosse Anzahl der hierhergehörigen, verschiedenartigen Bakterien in besondere, umschriebene Gruppen und Untergruppen einzuteilen, und so auf diesem noch etwas verworren liegenden Gebiete durch Aufstellung einer bestimmten Klassifikation bessere Uebersicht und Ordnung zu schaffen. *Löffler* hat dabei alle in Betracht kommenden, von ihm mit dem Sammelnamen Typhaceen bezeichneten Bakterienarten nach ihrem kulturellen Verhalten gegenüber seinen beiden Grünlösungen in die 3 Hauptgruppen der Typhaceae, der Josarceae und der Coleae zusammengefasst und bei diesen wieder nach dem serologischen Verhalten wie bezgl. der Pathogenität verschiedene Untergruppen aufgestellt.

Im Anschluss an die beiden Referate von *Babes* und *Löffler* wurde dann von Sektion I des Kongresses folgender Beschluss gefasst:

"Um die Erkenntniss der überaus wichtigen Bakterien der Typhaceen zu fördern, sollen eingehende vergleichende Untersuchungen der sämtlichen zu den Bakterien der Typhusgruppe gehörenden Organismen vorgenommen werden."

Mit diesen Untersuchungen wurden 7 Institute betraut, und bestimmt, dass über die Resultate auf dem nächsten internationalen Hygienekongress berichtet werden sollte.

Ich habe die Ehre, Ihnen über die im Kaiserlich Deutschen Reichsgesundheitsamt in Berlin unter Leitung meines Amtsvorgängers Geheimen Regierungsrat Professor Dr. *Uhlenhuth* ausgeführten, insbesendere die Bakterien der Paratyphusgruppe betreffenden Untersuchen Mitteilung zu machen.

Nach diesen Untersuchungen lassen sich in der Tat die verschiedenen der Typhusgruppe zuzurechnenden Bakterienarten auf Grund ihres Wachstums in den erwähnten Löffler'schen Nährmedien im allgemeinen nach 3 grossen Gruppen abteilen, wobei allerdings das Verhalten eines Stammes gegenüber den beiden Grünlösungen immer nur einen gewissen Anhaltspunkt über seine Stellung gibt, während

zu seiner näheren Bestimmung die Heranziehung weiterer Nährböden notwendig ist. Ebenso gibt eine erweiterte kulturelle Prüfung erst Aufschluss über die zahlreichen zwischen den einzelnen Gruppen stehenden Uebergangsvarietäten.

Im allgemeinen werden jetzt wohl ziemlich übereinstimmend für die genauere kulturelle Differentialdiagnose der der Typhusgruppe zuzurechnenden Bakterien ausser den beiden Löfflerlösungen hauptsächlich noch 9 andere Nährmedien, nämlich Milch, Lackmusmolke, die Nährlösungen *Barsiekow* I u. II, die Nährlösung nach *Hetsch*, Neutralrotagar, Orceinagar, sowie Traubenzucker- und Milchzuckerbouillon verwertet. Eine möglichst einheitliche und an allen in Betracht kommenden Stellen gleichmässig durchgeführte Benutzung solcher bestimmten Nährsubstrate könnte für die Erkenntnis der kulturellen Verhältnisse bei den hierhergehörigen Bakterien wie für die Erzielung übereinstimmender Resultate nur förderlich sein.

Bei den im Kaiserlichen Gesundheitsamt durchgeführten Untersuchungen sind die genannten Nährböden jedenfalls regelmässig herangezogen und die besten Erfahrungen damit gemacht worden, so dass dieses Vorgehen in jeder Hinsicht nur bestens empfohlen werden kann. Die nachstehende Tabelle enthält eine Zusammenstellung des Wachstums der hauptsächlichsten Vertreter der der Typhusgruppe zuzurechnenden Bakterien auf den angeführten Nährböden.

	Löffler I.	Löffler II.	Milch.	Lackmusmolke.	Barsiekow I. (Traubenzucker).
B. typhi.	Gerinnung, über dem Gerinsel klare, grüne Flüssigkeit, keine Schaumbildung.	Unverändert.	Keine Gerinnung.	Unverändert bzw. leichte Rötung, keine Trübung.	Rötung und Gerinnung.
B. dysenteriae Shiga-Kruse.	Unverändert.	Unverändert.	Keine Gerinnung.	Leichte Rötung, keine Trübung.	Rötung.
B. dysenteriae Flexner.	Zuweilen Gerinnung.	Unverändert.	Keine Gerinnung.	Leichte Rötung, keine Trübung.	Rötung.
B. paratyphi A.	Schmutzig-schaumige Gerinnung, Flüssigkeit trübe.	Unverändert.	Keine Gerinnung.	Rötung and Trübung.	Rötung und Gerinnung.
B. typhi suis [illegible].	Gerinnung, über dem Gerinsel klare, grüne Flüssigkeit, keine Schaumbildung.	Unverändert.	Keine Gerinnung.	Unverändert bzw. leicht gerötet, keine wesentliche Trübung.	Rötung.
B. [illegible].	Gerinnung, über dem Gerinsel klare, grüne Flüssigkeit, keine Schaumbildung.	Unverändert.	Keine Gerinnung.	Leicht gerötet, keine erhebliche Trübung.	Rötung und Gerinnung.
B. paratyphi B.	Schmutzig-schaumige Gerinnung, Flüssigkeit trübe.	Leichte Trübung.	Keine Gerinnung.	Zunächst gerötet alsdann Blaufärbung.	Rötung und Gerinnung.
B. enteritidis [illegible].	Schmutzig-schaumige Gerinnung, Flüssigkeit trübe.	Leichte Trübung.	Keine Gerinnung.	Zunächst gerötet alsdann Blaufärbung.	Rötung und Gerinnung.
B. coli.	Schmutzig-schaumige Gerinnung, Flüssigkeit trübe.	Schmutzig-schaumige Gerinnung, Flüssigkeit trübe.	Gerinnung.	Rötung und Trübung.	Rötung und Gerinnung.

	Barsiekow II. (Milchzucker).	Lackmusmannitnutroselösung nach Hetsch.	Traubenzuckerbouillon.	Milchzuckerbouillon.	Neutralrotagar.	Orceinagar.
B. typhi.	Unverändert.	Leichte Rötung, Gerinnung, keine Gasbildung.	Keine Gasbildung.	Keine Gasbildung.	Unverändert.	Unverändert.
B. dysenteriæ Shiga-Kruse.	Unverändert.	Unverändert.	Keine Gasbildung.	Keine Gasbildung.	Unverändert.	Unverändert.
B. dysenteriæ Flexner.	Unverändert.	Rötung, keine Gasbildung.	Keine Gasbildung.	Keine Gasbildung.	Unverändert.	Unverändert.
B. paratyphi A.	Unverändert.	Rötung, keine Gasbildung.	Gasbildung.	Keine Gasbildung.	Entfärbung, Gasbildung, Fluorescenz.	Entfärbung und Gasbildung.
B. typhi suis Glässer.	Unverändert.	Unverändert.	Zumeist keine Gasbildung.	Keine Gasbildung.	Schwankend zumeist unverändert, zuweilen wie verstehend.	Unverändert.
B. Voldagsen.	Unverändert.	Unverändert.	Zumeist Gasbildung.	Keine Gasbildung.	Entfärbung, Gasbildung, Fluorescenz.	Geringe Entfärbung.
B. paratyphi B.	Unverändert.	Rötung, Gerinnung, Gasbildung.	Gasbildung.	Keine Gasbildung.	Entfärbung, Gasbildung, Fluorescenz.	Entfärbung und Gasbildung.
B. enteritidis Gärtner.	Unverändert.	Rötung, Gerinnung, Gasbildung.	Gasbildung.	Keine Gasbildung.	Entfärbung, Gasbildung, Fluorescenz.	Entfärbung und Gasbildung.
B. coli.	Rötung und Gerinnung.	Rötung, Gerinnung, Gasbildung.	Gasbildung.	Gasbildung.	Entfärbung, Gasbildung, Fluorescenz.	Entfärbung und Gasbildung.

Es ist dabei allerdings zu erwähnen, dass die Tabelle nur eine schematische Uebersicht über die Wachstumsverhältnisse der einzelnen Bakterienstämme gibt, da bei Prüfung einer grossen Anzahl von Kulturen derselben Art, sich doch mitunter mehr oder weniger stark ausgesprochene Schwankungen bezgl. der Intensität des chemischen Reaktionsausfalles auf dem einen oder dem anderen Nährboden geltend machen können, die zum Teil allerdings auch von der Art der verwendeten Zuckerpräparate (*Ditthorn*) abhängen. Im allgemeinen darf man aber doch das in der Tabelle angegebene Verhalten als das für die einzelnen Bakterienarten charakteristische bezeichnen.

Vergleicht man an der Hand dieser tabellarischen Zusammenstellung das Wachstum der verschiedenen Bakterienarten, so lassen sich auch hier nach dem kulturellen Verhalten auf den genannten Nährböden 3 Hauptgruppen abtrennen, nämlich:

A. Die Typhusgruppe in engerem Sinne, der hinsichtlich der kulturellen Eigenschaften auch die verschiedenen Ruhrerreger nahestehen;

B. Die Gruppe des Bazillus Paratyphi B, des Bac. enteritidis Gärtner und der Kulturell gleichen Baktericuarten;

C. Die Gruppe der Colibakterien.

Dazwischen finden sich zahlreiche verschiedene Uebergangsvarietäten, welche sich in kultureller Hinsicht mehr der einen oder der anderen Gruppe näheren, und von denen in der Tabelle ausser dem zwischen der Typhusgruppe und der Gruppe des Paratyphus B stehenden Bazillus Paratyphi A zwei von *Glässer* und *Dammann* aus Schweinen isolierte und als Erreger einer besonderen bazillären Form der Schweinepest angesprochene Stämme, nämlich der Bazillus typhi suis Glässer und der Bazillus suipestifer Voldagsen aufgeführt sind. Auf diese beiden Bakterienarten wird bei Besprechung der Paratyphusgruppe noch des Näheren zurückzukommen sein.

Der Gruppe B, mit welcher sich hauptsächlich die weiteren Ausführungen befassen sollen, gehören nun ausser dem eigentlichen Bazillus Paratyphi B Schottmüller und den bei den Gruppenerkrankungen in Breslau, Meirelbeck, Düsseldorf, Sirault, Aertryck, Neunkirchen, Greifswald u. s. w. isolierten Paratyphus B gleichen Stämmen, der Bazillus typhi murium, der Bazillus der Psittacose, der Bazillus suipestifer und, wie erwähnt, ausserdem der Bazillus enteritidis Gärtner, die bei den Epidemien von Moorseele, Gent, Rumfleth, Haustedt, Brügge gefundenen, ihm gleichen Bakterien, sowie die als Rattenschädlinge bekannten, von *Danysz*, *Dunbar*, *Issatschenko* u. a. bei Rattenepizootien gezüchteten Kulturen an. Ebenfalls ihr zuzurechnen sind ferner die bei den Fleischvergiftungen in Lassan und Barth gewonnenen Kulturen, der Bazillus Paratyphi C. (*Uhlenhuth*, *Hübener*) sowie die weiteren von zahlreichen Autoren (*Titze*, *Weichel*, *Schmidt*, *Müller*, *Sobernheim*, *Seligmann*, *Jakobits* u. *Kayser*, *Rimpau*, *Haendel* u. *Gildemeister*, *Messerschmidt* u. a.) gefundenen Stämme, welche sich kulturell ebenfalls vollkommen wie der Bazillus Paratyphi B und der Bazillus enteritidis Gärtner verhalten, aber zu diesen in serologischer Hinsicht keine Beziehung aufweisen.

Die Gruppe umfasst also im Wesentlichen die Stämme, welche man früher mit verschiedenen Sammelnamen wie Hog-Cholera-, Salmonella-, Flügge-Kaensche Gruppe und in neuerer Zeit meist unter der Bezeichnung Paratyphusgruppe zusammengefasst hat. Nicht verfehlen möchte ich an dieser Stelle darauf hinzuweisen, dass unser sehr verehrter Vorsitzender, Herr Professor *Theobald Smith* der erste war, der im Jahre 1894, noch vor Entdeckung der spezifischen Fleischvergiftungsbakterien die verwandtschaftlichen Beziehungen des Hogcholerabazillus zu andern Bakterien auf Grund morphologischer und biologischer Merkmale festzustellen versuchte. Er war es, der die Hogcholera- oder Salmonellagruppe aufstellte, in die er ausser dem Bazillus suipestifer den Bazillus typhi murium, den Bazillus enteritidis Gärtner und einen aus Abortus einer Stute gezüchteten Bazillus rechnete. [1] Vgl. hiezu auch die in neuester Zeit erschienene Arbeit von de Jong, Über einen Bacillus der Paratyphus

B Enteritisgruppe als Ursache eines seuchenhaften Abortus der Stute. Centralbl. f. Bakteriologie, Abt. I, Orig. Bd. 67, Heft. 3, S. 148.

Allerdings dürfte es sich auch unseres Erachtens entsprechend der neuerdings von *Soberheim* aufgestellten Forderung empfehlen, diese Sammelnamen in erster Linie nur auf die Stämme, welche sich nicht nur kulturell, sondern auch serologisch dem Bazillus Paratyphi B Schottmüller gleich verhalten, zu beschränken, und nicht ohne weiteres auch auf die in ihrem serologischen Verhalten von den Paratyphusbazillen verschiedenen Kulturen, wie zum Beispiel die Stämme der Gärtnergruppe auszudehnen, da es sich in beiden Fällen zwar um nahe verwandte, aber doch im allgemeinen einheitlich für sich abgrenzbare Bakterienarten handelt, wenn gleich sich bei ihnen, wie neuere Untersuchungen (*Sobernheim* u. *Seligmann*, *Lentz*, *Rimpau*, *Haendel* u. *Gildemeister*, *Bärthlein* u. a.) gezeight haben, in dieser Hinsicht auch in ihrem serologischen Verhalten auffallende Schwankungen und eigenartige Verschiebungen geltend machen können.

Trotz dieser später noch zu besprechenden Veränderlichkeiten wird aber doch daran festzuhalten sein, die Paratyphus- und Gärtnerbakterien als besondere mit Hilfe der Immunitätsreaktionen differenzierbare Arten anzusehen, wie dies zuerst von *Uhlenhuth* festgestellt worden ist. In morphologischer und kultureller Hinsicht lassen sich allerdings bei ihnen nach den bisherigen Untersuchungen keine konstanten, deutlich ausgesprochenen Unterschiede feststellen. Die von *Babes* erwähnte Verschiedenheit in der Begeisselung des Paratyphus B- und des Gärtnerbazillus ist nicht so deutlich ausgesprochen, dass sie für eine Differenzierung verwertet werden könnte, ebenso sind die von *Babes* erwähnten kulturellen Unterschiede, wonach die Gärtnerbazillen Neutralrot und Orcein energischer verfärben wie die Paratyphusbakterien nicht so gleichmässig und durchgreifend, dass danach eine Trennung vorgenommen werden könnte. Auch die von einzelnen Autoren (*Savage*, *Schern* u. a.) auf besonderen Nährböden beobachteten Differenzen finden sich nicht konstant.

Dagegen scheinen in anderer Hinsicht vielleicht doch durchgreifendere kulturelle Unterschiede bei beiden Gruppen zu bestehen. Nach von *Bärthlein* im Kaiserlichen Gesundheitsamt durchgeführten Untersuchungen lassen sich nämlich anscheinend bei allen Bakterienarten unter bestimmten Bedingungen eigenartige, plötzlich einsetzende Abspaltungsvorgänge feststellen, welche wir als Mutationsvorgänge aufzufassen geneigt sind, und die in der Weise in Erscheinung treten, dass auf der gewöhnlichen Agarplatte dieselbe Bakterienart gleichzeitig in verschiedenen Kolonieformen wächst, welche sich jeweils wieder aus morphologisch differenten Bakterien

zusammensetzen. Die mutierten Kolonieformen zeigen nun bei den einzelnen Bakterienarten im allgemeinen—auf die genaueren Einzelheiten kann im Rahmen dieses Referates nicht näher eingegangen werden, es sei vielmehr verwiesen auf die in Band 40 der Arbeiten aus dem Kaiserlichen Gesundheitsamt erschienene Arbeit von *Bärthlein*—ein charakteristisches Aussehen, so dass in manchen Fällen schon aus der Koloniebildung in gewissem Sinne ein Schluss auf die Zugehörigkeit einer Kultur zu einer bestimmten Bakterienart gezogen werden kann.

Die mutierenden Gärtnerstämme wachsen nun auf der Agarplatte regelmässig auch in für sie ganz charakteristischen, kleinen, gelbweissen, bei durchfallendem Licht stark perlmutterartig irisierenden Kolonien, während von den Bakterien der Paratyphusgruppe derartige Formen nicht gebildet werden. Nur der Bacus der Pspittacose macht eine Ausnahme, auch bei ihm entwickeln sich bei der Mutation dem Koloniëntyp der Gärtnerstämme entsprechende Kolonieformen.

Von dieser Ausnahme abgesehen scheint hier aber ein bemerkenswerter Unterschied in dem Verhalten der Stämme der Paratyphus- und Gärtnergruppe wenigstens nach den bisherigen Beobachtungen zu bestehen.

Wie liegen nun die Dinge bei gesonderter Betrachtung der der Gärtner- und Paratyphusgruppe in engerem Sinne zuzurechnenden Bakterienarten?

Wenn wir uns zunächst der Paratyphusgruppe zuwenden, so hat man auch hier zunächst geglaubt, durch kulturelle Unterschiede den Bac. Paratyphi B Schottmüller von den bei Fleischvergiftungen gefundenen Paratyphus B-gleichen Stämmen und den tierpathogenen Arten abtrennen zu können. Die Beobachtung von *Babes*, wonach die Letzteren und die Fleischvergiftungsstämme Malachitgrün stärker aufhellen wie die eigentlichen menschlichen Paratyphuskulturen ist zwar nicht selten zutreffend, gestattet aber keineswegs eine durchgreifende Scheidung. Ebenso hat sich die Feststellung von *v. Drigalski* sowie von *Fischer*, dass sich frisch isolierte Paratyphus B Stämme des Menschen auf der Blauplatte durch die Bildung besonderer Kolonien mit deutlicher Randumwallung und eingesunkenem Zentrum auszeichnen, bei späteren Untersuchungen (*Kutscher* u. *Meinicke*, *Trautmann* u. a.) nicht als konstantes Differenzierungsmerkmal verwerten lassen.

Auch die interessanten Befunde *R. Müllers*, wonach es bei den Kolonien frisch aus dem Menschen isolierter Paratyphusstämme zur Bildung eines eigenartigen Schleimwalles und auf Raffinoseagar zur Entstehung kleiner, den Kolonien aufsitzender Knötchen kommt, während die anderen Stämme, die Mäusetyphus- und die Schweinepestkulturen nur knopflose Kolonien entwickeln, sind noch nicht bezgl.

ihrer Konstanz so sicher gestellt, dass schon jetzt ein bestimmtes Urteil über den differentialdiagnostischen Wert dieser Erscheinungen abgegeben werden kann. Bei den Untersuchungen *Bärthleins* über die auf der Agarplatte zu beobachtenden Mutationsvorgänge haben sich jedenfalls nach den bisherigen Beobachtungen keine durchgreifenden Unterschiede bei den verschiedenen Stämmen der Paratyphusgruppe feststellen lassen, und man kann sich nach allem nur dahin aussprechen, dass auf Grund kultureller Merkmale eine Scheidung des Bac. Paratyphi B von den Fleischvergiftungsstämmen und den tierpathogenen Arten der Gruppe auch heute nicht möglich ist. Aehnlich liegen auch die Dinge bezgl. der Möglichkeit einer Differenzierung mit Hilfe der biologischen Immunitätsreaktionen. Schon die ersten Untersuchungen von *Trautmann*, *Uhlenhuth*, *Kutscher* u. *Meinicke*, *Bock* u. a. haben gezeigt, dass auch bei diesen Prüfungen eine Trennung zwischen dem Paratyphus B Bazillus, den entsprechenden Fleischvergiftern und den tierpathogenen Arten nicht möglich ist. Mit Hilfe des Castellanischen Absättigungsversuchs wollen allerdings *Nishino* zwischen dem Paratyphus B Bazillus und dem Mäusetyphusbazillus, sowie *Bainbridge*, *Savage* u. a. zwischen den Ersteren und dem Bac. suipestifer Unterschiede gefunden haben. Auch kann in der Tat schon nach früheren von *Bock* im Kaiserlichen Gesundheitsamt ausgeführten Untersuchungen diese Methode bei Verwendung bestimmter Stämme derartige Ergebnisse liefern, sie versagt aber nach den Feststellungen von *Uhlenhuth* u. *Hübener*, sobald die Versuche an einer sehr grossen Zahl von Kulturen vorgenommen werden.

Entsprechend haben auch die in neuerer Zeit mit der Komplementbindung (*Altmann*, *Ballner* u. *Reibmayer*) und mittelst der Anaphylaxie (*Lieverato*) ausgeführten Differenzierungsveruche zu negativen Ergebnissen geführt.

Trotzdem wir so nicht in der Lage sind, mit Hilfe der bisher angewandten Methoden die einzelnen Bakterienarten der Paratyphusgruppe sicher zu unterscheiden, so können wir sie andererseits aber auch noch nicht ohne weiteres alle, namentlich auch die verschieden tierpathogenen Stämme, als eine mit dem menschlichen Paratyphus B Bazillus vollkommen einheitliche Art auffassen, da sich doch bei ihnen zum Teil im pathogenen Verhalten, zum Teil auch in serologischer Hinsicht eigenartige, wenn auch nicht durchgreifende Abweichungen geltend machen, welche noch weiterer Klärung bedürfen und zu einer gewissen Vorsicht bezgl. der Beurteilung in dieser Hinsicht mahnen. Ursprünglich hatte man dazu geneigt, als Grundlage für eine Einteilung und Abtrennung der einzelnen Arten ihr pathogenes Verhalten zu verwerten, es hat sich dann aber ergeben, dass auch auf dieser Basis eine scharfe Trennung nicht durchzuführen ist. Durch die Versuche zahlreicher Autoren (*Kutscher-*

Meinicke, *Shibayama*, *Uhlenhuth-Hübener* u. a.) wurde vielmehr festgestellt, dass grundsätzliche, durchgreifende Unterschiede bei den verschiedenen Arten bezgl. ihrer Pathogenität für kleinere Versuchstiere sowie für unsere Schlachttiere nicht bestehen, insbesondere hat *Schmitt* den Nachweis erbracht, dass auch menschliche Paratyphusstämme eine Infektion der Schlachttiere bewirken können. Ebenso hat es sich ferner gezeigt, dass auch den tierpathogenen Arten eine gewisse Pathogenität für den Menschen zukommt. So ist nicht nur die Möglichkeit einer Infektion des Menschen durch Mäusetyphuskulturen und Rattenschädlinge, sondern auch durch Schweinepestbazillen sowie durch den Bazillus der Psittacose durch die Beobachtungen von *Trommsdorff*, *Fleischanderl*, *Meyer*, *Shibayama*, *Ungar*, *Babes* und *Busila*, *Handson* und *Williams*, *Silberschmidt*, *Rochi* und *Tiberti*, *v. Slooten*, *Dewes* u. a. Autoren erwiesen worden.

Vom Deutschen Reich und von Preussen sind im Jahre 1905, vom Oesterreichischen Ministerium des Innern im Jahre 1910 Verhaltungsmassregeln zur Verhütung von Gesundheitsschädigungen durch Beschäftigung mit Mäusetyphusbazillen bekannt gegeben worden (vergl. Veröffentlichungen des Kaiserlichen Gesundheitsamtes 1905 S. 332 und S. 683, sowie 1910 S. 591).

Hier möge auch das Resultat eines nicht veröffentlichten Selbstversuches, den Reg. Rat. Dr. *Beck* im Jahre 1903 im Kaiserlichen Gesundheitsamt angestellt hat, Erwähnung finden.

Beck nahm 2 ccm einer 48 stündigen bei Zimmertemperatur in Magermilch gewachsenen Reinkultur von Mäusetyphusbazillen mit 100 ccm lauwarmen Thees vermischt zu sich. Am folgenden Tage wurde öfteres Gurren im Leibe verspürt; am 3. und 4. Tage erfolgte geringer Durchfall mit 3–4 maliger schmerzloser Entleerung von dünnflüssigem gallig gefärbtem Stuhl. Das Allgemeinbefinden war in keiner Weise verändert, vor allem bestand keine Temperatursteigerung, der Appetit war unverändert gut. Im Stuhlgang waren am 3. Tage nach der Aufnahme reichliche Mengen von Mäusetyphusbacillen nachweisbar. Im Ausstrich auf Agar-Agar entwickelte sich eine Reinkultur dieser Stäbchen. Diese konnten noch am 10. Tage nach Beginn des Versuchs durch ein besonderes Anreicherungsverfahren im Stuhl festgestellt werden, waren aber vom 15. Tage ab verschwunden. Eine an dem selben Tage angestellte Agglutinationsprobe mit dem Serum der Versuchsperson ergab noch bei einer Verdünnung von 1 : 300 eine deutliche Agglutination.

Andererseits ist aber auch zuzugeben, dass in gewisser Hinsicht eine besondere Pathogenität für bestimmte Tierarten bei den einzelnen Untergruppen doch stärker hervortritt. Es kann sich bei dieser Tatsache zwar nur um eine allmählich erworbene Anpassungserscheinung handeln, sie könnte aber unter Umständen doch auch in

bestimmten, uns bisher noch unbekannten Differenzen bei den betr. Arten begründet sein. In dieser Hinsicht ist eine neuerdings von *Haendel* u. *Gildemeister* mitgeteilte Beobachtung vielleicht von Interesse, wonach agglutinierende Sera, welche mit den bereits erwähnten von *Glässer* u. *Dammann* aus Schweinen isolierten Paratyphusähnlichen Stämmen gewonnen waren, verschiedene von ihnen geprüfte Pestiferstämme ebenfalls bis zur Titergrenze agglutinierten, Paratyphus B Stämme dagegen nicht oder doch nicht in nennenswerter Weise beeinflussten. Diese Beobachtung war besonders auffallend, weil der Bazillus typhi suis und der Dammannsche Bazillus sich kulturell nicht nur untereinander, sondern auch deutlich ausgesprochen von dem Wachstum der Pestifer- und Paratyphusstämme unterscheiden. Der Bazillus Glässer lässt Lackmusmolke, die *Hetsch*'sche Lösung, sowie Neutralrot und Orcein unverändert, während der Bazillus Voldagsen Lackmusmolke und den *Hetsch*'schen Nährböden ebenfalls unverändert lässt, oder die ersteren nur leicht rötet, dagegen Neutralrot und Orcein deutlich aufhellt. Auf Traubenzuckerbouillon zeigen die Kulturen insofern ein schwankendes Verhalten, als beide hier bald Gasbildung bewirken bald nicht.

Haendel u. *Gildemeister* konnten ihre Beobachtungen ferner noch dahin ergänzen, dass auch Sera, welche sie mit von ihnen aus schweinepestkranken Schweinen isolierten Paratyphus B gleichen, aber für Paratyphus- und Gärtnersera inagglutinablen Stämmen hergestellt hatten, das gleiche Verhalten zeigten und ausschliesslich *Glässer*- und *Voldogsen*-Stämme und, wenn auch nur in geringerem Grade, Pestiferkulturen, nicht aber Paratyphus stämme agglutinierten. Diese Befunde sind an einem grossen Kulturmaterial von *Teodorascu* weiter verfolgt und bestätigt worden.[1] Es hat danach den Anschein, als ob sich unter den Paratyphus B- und Pestiferstämmen nach dem agglutinatorischen Verhalten gegenüber den betr. heterologen Seris 2 Gruppen abtrennen lassen, von denen die eine, welche sich meist aus von Schweinen und Schlachtwaren gewonnenen Kulturen zusammensetzt, höher beeinflusst wird wie die andern, welche hauptsächlich aus von Menschen gezüchteten Paratyphus B Stämmen besteht. Allerdings kommen einzelne Ausnahmen vor, sodass bei einer derartigen Trennung nach dem agglutinatorischen Verhalten gegenüber den heterologen Seris vereinzelte aus dem Menschen gewonnene Stämme der Pestifergruppe und umgekehrt einzelne aus Schweinen stammende Kulturen der Para-Typhus B Gruppe zuzurechnen sind.

Es müssen aber auch hier erst die Ergebnisse noch weiterer Untersuchungen abgewartet werden, ehe über den differentialdiagnostischen Wert dieser Erscheinung ein bestimmtes Urteil gefällt werden kann. Zu berücksichtigen ist dabei, dass bei den Glässer- und Voldagsenstämmen und ebenso bei den Paratyphusgleichen aber für Para-

typhussera inagglutinablen Kulturen offenbar in dem agglutinatorischen Verhalten auffallende Veränderungen auftreten können. *Dammann* und *Stedefeder* hatten ursprünglich angegeben, dass ihre Kulturen nicht durch Pestifersera beeinflusst wurden, und dass umgekehrt Voldagsensera auch Pestiferstämme nicht agglutinierten. *Uhlenhuth*, *Haendel* u. *Gildemeister* haben diese Angabe bestätigt, sie beobachteten aber, dass die Voldagsenstämme sich bei der Fortzüchtung in ihrem Verhalten änderten, später durch Pestifersera agglutiniert wurden und auch Sera erzeugten, welche Pestiferstämme gleichfalls beeinflussten. Gleichzeitig machten sich bei den betr. Kulturen auch Veränderungen im kulturellen Verhalten bemerkbar. Später haben *Haendel* u. *Gildemeister* auch Voldagsenstämme gefunden, welche sofort nach der Isolierung aus dem Schwein bereits von Pestiferseris agglutiniert wurden. Die betreffenden Stämme verhalten sich demnach in kultureller und agglutinatorischer Hinsicht auffallend labil. Das gleiche gilt nun wenigstens bzgl. des agglutinatorischen Verhaltens auch für die Paratyphusgleichen aber ursprünglich für Paratyphussera unempfindlichen Stämme. Bei den unter der Leitung *Uhlenhuths* im Kaiserlichen Gesundheitsamt durchgeführten Untersuchungen über Schweinepest sind eine grosse Anzahl derartiger Kulturen aus Schweinen isoliert und lange weiter verfolgt worden. Dabei hat es sich gezeigt, dass nicht selten solche Stämme in Laufe der Zeit später doch durch Pestifer- oder Gärtner-Sera agglutiniert wurden, wenn sie auch ihre agglutinatorische Sonderstellung zunächst ein Jahr oder noch länger behauptet hatten. Andere ebenso lange in Beobachtung stehende Kulturen dagegen sind für Paratyphus- und Gärtner-Sera ständig inagglutinabel geblieben, wurden aber zum Teil von Glässer und Voldagsenseris beeinflusst.

Ueber ganz ähnliche Schwankungen auch bei typhischen Paratyphus B- und Gärtnerstämmen war schon vorher von *Sobernheim* und *Seligmann* berichtet worden. Diese Autoren hatten die Beobachtung gemacht, dass typische Paratyphusstämme ihre Agglutinierbarkeit mit Paratyphusseris allmählich immer mehr einbüssten, und dafür in immer zunehmendem Masse von Gärtnerseris beeinflusst wurden, sodass sie schliesslich mit den ersteren so gut wie nicht mehr und nur noch mit den letzteren reagierten. Gleichzeitig machten sich bei den betr. Stämmen auch kulturelle Veränderungen bemerkbar, indem die Kulturen auf der Agarplatte ganz anders aussehende Kolonien bildeten wie zuvor. Dagegen hatten sie ihren Artcharakter als Paratyphusstämme insofern bewahrt, als mit ihnen hergestellte Immunsera nur Paratyphusbakterien, nicht aber Gärtnerkulturen agglutinierten. Noch auffallender waren die bei Gärtnerstämmen festgestellten Veränderungen. Im Allgemeinen liegen zwar auch bei den Gärtnerbakterien die Verhältnisse ähnlich, wie sie

vorstehend für die verschiedenartigen Bakterien der Paratyphusgruppe geschildert wurden. Auch bei den einzelnen Bakterienarten der Gärtnergruppe, den Rattenschädlingen, den Kälberruhrstämmen (*Jensen*, *Uhlenhuth-Hübener*, *Titze-Weichel* u. a.) und den von Menschen stammenden Kulturen ist eine scharfe, durchgreifende Trennung und Einteilung in bestimmt umschriebene Untergruppen auf Grund kultureller Differenzierungsmerkmale oder mit Hilfe der Immunitätsreaktionen nach den Untersuchungen von *Uhlenhuth*, *Xylander*, *Steffenhagen*, *Schern*, *Titze*, *Weichel* u. a. nicht möglich.

Allerdings lassen sich anscheinend nach den Feststellungen von *Sobernheim* und *Seligmann* auch unter den Gärtnerstämmen bei Benutzung bestimmter Sera in gewisser Hinsicht nach dem Verhalten bei der Agglutination und Complementbindung 2 Untergruppen abtrennen, von denen die eine hauptsächlich Rattenschädlinge umfasst. Auch die von *Beniasch* mit der Säureagglutination erhaltenen Befunde weisen auf gewisse Differenzen hin. Die Ergebnisse sind aber doch nicht so scharf und eindeutig, dass sie zu einer vollständigen Abtrennung der 2 Gruppen ausreichen, zumal eine grosse Anzahl anderer Sera beide Typen vollständig gleichmässig beeinflussen. Dazu kommt, dass man nach den von *Sobernheim* u. *Seligmann* erhobenen ausserordentlich auffallenden Befunden bei der Gärtnergruppe mit einer noch viel stärkeren Veränderlichkeit einzelner Stämme rechnen muss, als bei den Paratyphusbakterien.

Sobernheim u. *Seligmann* konnten nämlich aus 2 ursprünglich typischen Gärtnerstämmen, den Kulturen Rumfleth u. Haustedt eine ganze Reihe von Tochter- und Sonderstämmen gewinnen, welche zum Teil nach ihrem serologischen und kulturellen Verhalten noch Beziehungen zur Gärtnergruppe aufwiesen, zum Teil aber vollständig andersartige Kulturen darstellten und sich teils dem Bac. Paratyphus A oder dem Coli mutabile ähnlich, teils vollkommen wie Typhusbazillen verhielten. Diese ausserordentlich auffallenden Beobachtungen können vorläufig nur als solche vermerkt werden, sie bedürfen noch weiterer Klärung, ehe eine bestimmte Beurteilung dieser Befunde möglich sein wird. Das Eine lässt sich allerdings schon heute mit Sicherheit sagen, dass sich unter den Stämmen der Paratyphus- und noch mehr der Gärtnergruppe Kulturen finden, bei welchen biologische Umwandlungen nachzuweisen sind, und die sowohl in ihrem kulturellen wie auch serologischen Verhalten ausserordentlich eigenartige und auffallende Schwankungen und Veränderungen zeigen können.

Neben diesen zunächst hauptsächlich ein wissenschaftliches Interesse beanspruchenden, bemerkenswerten Befunden über das biologische Verhalten der Paratyphus- und Gärtnerbakterien haben die neueren Forschungen über diese Bakteriengruppe auch zu in

praktischer Hinsicht wertvollen und namentlich für die Epidemiologie der durch diese Erreger bedingten Krankheiten wichtigen Ergebnissen geführt.

Bei den im Kaiserlichen Gesundheitsamt unter der Leitung *Uhlenhuths* durchgeführten Untersuchungen über die Schweinepest wurde die Tatsache festgestellt, dass im Darminhalt gesunder Schweine Bazillen vorkommen können, welche von echten Pestifer- und Paratyphusbakterien nicht zu unterscheiden waren. Auf Grund dieser Beobachtung haben *Uhlenhuth* und seine Mitarbeiter schon in ihrer ersten Arbeit über das Wesen der Schweinepest die Bedeutung dieser Feststellung für die Epidemiologie des Paratyphus und der Fleischvergiftungen hervorgehoben und darauf hingewiesen, dass nach diesen Befunden nicht nur ein gelegentliches Uebergehen dieser Bakterien auf die Schlachtprodukte des Schweines anzunehmen sei, sondern dass man wohl auch mit ihrem Vorkommen bei anderen Tieren und mit ihrer weiteren Verbreitung in der Aussenwelt durch die Excremente der Tiere zu rechnen habe. *Uhlenhuth* hat sofort nach dieser Richtung Versuche aufgenommen, welche die geäusserte Vermutung vollauf bestätigten. Gemeinsam mit *Hübener* konnte er in verschiedenen Wurstproben, in den Ausscheidungen gesunder Menschen, welche von solchen Wurstwaren genossen hatten, und in einigen Milchproben derartige Bakterien nachweisen. *Uhlenhuth* u. *Hübener* fanden, dass diese Bakterien ferner bei Fällen von Kälberruhr vorkommen und auch im Darminhalt gesunder Kälber festzustellen sind. Bei vergleichenden Untersuchungen einer grösseren Zahl als Erreger der Kälberruhr beschriebenen Stämme konnten sie zeigen, dass unter diesen der Jensen'sche Paracolibazillus sich wie der Bac. enteritidis Gärtner, verschiedene andere Kulturen wie Paratyphusstämme verhielten. Diese Ergebnisse sind durch die Untersuchungen von *Titze* u. *Weichel*, *Langkau*, *Schmitt*, bestätigt worden. Auch sonst sind bei kranken Kälbern, Kühen und anderen grösseren Tieren von zaldreichen Autoren wie *Langer*, *Bugge*, *Junack*, *Ledschbor*, *Dieudonné*, *Schmitt*, *Zeller*, *Zwick u. Weichel*, *Fally*, *Riemer*, *Edenhuizen*, *Franke*, *Zwick* u. a. Paratyphus- und Gärtnerbazillen gleiche Bakterien gefunden worden. Ferner sind solche Bakterien nachgewiesen bei Affen (*Tromsdorff* u. a.), bei Papageien (*Eckersdorff*, *Drewes*, *Selter*) bei Sperlingen (*Tartakowsky* u. *Sacquépée*) und bei Kanarienvögeln (*Pfeiler*, *Adam* und *Meder* u. a.). Bei der Pseudotuberkulose des Meerschweinchens wurden sie von *Neisser*, *Böhme* und *Eckersdorff*, von *Dieterlen* und *Bofinger* festgestellt, nachdem schon vorher *Theobald Smith*, *van Ermengem* und *Durham* auf das Vorkommen zur Paratyphusgruppe gehöriger Mikroorganismen bei dieser Erkrankung des Meerschweinchens aufmerksam gemacht hatten. Sie wurden ausserdem gefunden bei Epizootien von Ratten und Mäusen, sowie im Kot und im Organismus von gesunden Indi-

viduen dieser Tierarten (*Uhlenhuth, Xylander, Schern, Trautmann, Mühlens, Dahm* und *Fürst, Zwick* u. a.), ferner im Kot von Meerschweinchen und Kaninchen (*Morgan* und *Smallmann*) im Darminhalt von Gänsen (*Heusser*), im Hundekot (*Vallet u. Rimbaud*), endlich im Darminhalt von Fliegen (*Nicoll* und *Torrey*).

Von besonderer Bedeutung ist ihr Nachweis bei gesunden Schlachttieren, bei unverdorbenen Fleisch- und Wurstwaren und anderen Nahrungsmitteln. Ausser den schon erwähnten Befunden von *Uhlenhuth* und *Hübener* wurden sie von *Grabert, Eckert, Conradi, Trautmann, Seiffert, Schmidt, Sobernheim u. Seligmann, Rimpau, Buthmann, Rommeler* und von anderen Autoren im Darminhalt, bezw. in den Organen von gesunden Schlachttieren oder in Schlachtwaren gefunden.

Im Wasser und Eis sind sie ebenfalls verschiedentlich so von *Forster, Sternberg, Gäthgens, Georg Mayer, Conradi, Rommeler* u. a. und in Milchproben von *Hübener, Conradi, Klein und Georg Meyer* nachgewiesen worden. In Uebereinstimmung mit diesen Befunden konnten auch in den Faeces gesunder Menschen, bei denen nachweisbare Beziehungen mit Paratyphusfällen oder mit an Fleischvergiftung erkrankten Personen nicht nachzuweisen waren derartige Bakterien von *Hübener* und *Viereck, Conradi, Kayser, Gäthgens, Rimpau, Küster Marmann* u. a. aufgefunden werden. Dass bei diesen Befunden die Ausschiedung der mit Nährungsmitteln aufgenommenen Bakterien in Betracht kam, konnte *Conradi* dadurch experimentell erweisen, dass er eine mehrköpfige Familie zum Genuss von derartige Bakterien enthaltendem rohem Hackfleisch veranlasste und darnach in den Stuhlgängen und in dem Blut der Frau die betreffenden Bakterien nachweisen konnte, ohne dass irgend eine Störung des Allgemeinbefindens bei einer der Personen zu beobachten gewesen wäre. *Conradi* bezeichnet diese Art der Bakterienausscheidung als alimentäre Ausscheidung. Im allgemeinen währt die Ausscheidung der Keime in solchen Fällen nur kurze Zeit, und die Anzahl der Bakterien ist gering. Allerdings liegen nun auch eine Reihe von Angaben von *Seiffert, Trautmann, Amako, Aumann, Sobernheim, Schmidt, König* u. a. vor, wonach auch bei umfangreichen Untersuchungen ein solch verbreitetes Vorkommen dieser Bakterien im Darminhalt und den Organen der Schlachttiere, bei Schlachtwaren und anderen Nahrungsmitteln etc., sowie beim Menschen nicht festgestellt werden konnte. In England wird von *Bainbridge* und *Brion* die Existenz der gelegentlichen Ausscheider ganz in Abrede gestellt. Diese sich zum Teil widersprechenden Ergebnisse finden nach der Auffassung von *Trautmann, Sobernheim, Uhlenhuth* und *Hübener* darin ihre Erklärung, dass bei der Verbreitung dieser Bakterien offenbar mit regionären Verschiedenheiten und vielleicht auch zeitlichen Einflüssen zu rechnen ist.

Sobernheim macht dabei zugleich darauf aufmerksam, dass auch bezgl. des Verlaufs der Paratyphuserkrankungen in gewisser Hinsicht regionäre Verschiedenheiten sich insofern bemerkbar machen, als in den nördlichen Teilen des Reiches gegenüber dem Südwesten die Paratyphuserkrankungen hauptsächlich als schwere Nahrungsmittelvergiftungen oder als akute, choleraähnliche Anfälle, dagegen nur selten in der im Südwesten des Reiches überwiegender hervortretenden, mehr chronischen Typhus-ähnlichen Form des eigentlichen Paratyphus verlaufen.

Auch bei den im Kaiserlichen Gesundheitsamt durchgeführten Untersuchungen über Schweinepest ergaben sich Anhaltspunkte dafür, dass sich bei dieser durch ein filtrierbares Virus bedingten Krankheit ebenfalls bzgl. der Art der jeweils dabei auftretenden, dem Bazillus Pestifer oder dem Gärtnerbazillus gleichen oder ähnlichen Begleitbakterien anscheinend regionäre Verschiedenheiten geltend machen können. Wie dem auch ist, jedenfalls ist daran nicht zu zweifeln, dass in verschiedenen Gegenden ohne nachweisbaren Zusammenhang mit Fleischvergiftungen oder Paratyphuserkrankungen bei Menschen und Tieren bei Schlachtprodukten und anderen Nahrungsmitteln u. s. f. nicht selten Bakterien gefunden worden sind, welche sich von den Erregern des Paratyphus, in manchen, allerdings bisher weniger zahlreichen Fällen von Gärtnerbazillen nicht unterscheiden lassen.

Eine andere Frage ist es nun allerdings, wie die Pathogenität dieser Bakterien für den Menschen zu beurteilen ist, ob ihnen eine dem Paratyphus- oder Gärtnerbazillus gleiche oder in Vergleich zu diesen geringere oder überhaupt keine Pathogenität zukommt. Wie schon vorher ausgeführt worden ist, beweist der Umstand, dass wir in keiner Weise in der Lage sind, die betreffenden Bakterien von den echten Paratyphus- oder Gärtnerbazillen zu unterscheiden, noch nicht mit Sicherheit, dass wir es bei ihnen mit Bakterien zu tun haben, die den genannten Infektionserregern vollkommen gleich zu stellen sind. Es spricht vielmehr manches dafür, dass ihnen im allgemeinen nur eine verhältnismässig geringe Pathogenität zukommt, da sonst bei ihrem häufigen Vorkommen die Zahl der Paratyphus- und Gärtnerinfektionen eine weit höhere sein müsste, als sie nach allen Erfahrungen bisher beobachtet wurde. Andererseits haben wir aber auch keinerlei Anhaltspunkte, um mit Sicherheit ausschliessen zu können, dass nicht derartige Bakterien unter uns noch unbekannten Bedingungen für den Menschen jederzeit pathogen zu werden vermögen. Es ist dabei besonders zu berücksichtigen, dass auch bei den echten Paratyphus- und Gärtnerbazillen, wie wir wissen, ausserordentlich grosse Virulenzunterschiede und Virulenzschwankungen vorkommen. Es ist hier ferner hinzuweisen auf die Beobachtungen von *Uhlenhuth*, *Haendel* und *Steffenhagen*, sowie von *Zwick* und *Weichel*, wonach Ratten und

Mäuse lange Zeit den Gärtnerbazillen gleiche Bakterien in völlig gesundem Zustande ausscheiden können, sofort aber an einer Gärtnerinfektion erkranken und zu Grunde gehen, sobald sie nach Impfung mit einem Tumor in ihrem Kräftezustand zurückgekommen oder unter ihnen nicht zusagende Fleischnahrung gesetzt werden. Auch können dann solche Tiere die Infektion auf andere gesunde Ratten und Mäuse übertragen und zu ausgedehnten Epizootien Anlass geben. Es spricht nichts gegen die Annahme, dass auch beim Menschen durch derartige zunächst scheinbar avirulente Bakterien unter Bedingungen, die wir nicht zu übersehen im Stande sind, schwere Infektionen ausgelöst werden können. Aus den bei der Erforschung der Schweinepest gewonnenen Erfahrungen wissen wir, dass auch bei dieser Krankheit gerade Bakterien der Pestifer- und Gärtnergruppe sowie ihnen ähnliche Bakterienarten unter dem Einfluss des filtrierbaren Virus eine Virulenzsteigerung erfahren und sekundäre bakterielle Infektionen veranlassen können. Auch beim Menschen sind schon entsprechende Erfahrungen gemacht und z. B. unter dem Einfluss von Scharlach-(*Rimpau*) und Gelbfiebererkrankungen (*Sanarelli* u. a.) ein Virulentwerden derartiger Bakterien und nachträgliche Sekundärinfektionen beobachtet worden.

Man wird deshalb nach allem an dem Vorkommen der betreffenden Bakterien doch nicht achtlos vorüber gehen dürfen, sondern die gegen Paratyphus und Fleischvergiftungen gerichteten Massnahmen auch auf sie ausdehnen müssen. Bei der im Südwesten des Reiches eingerichteten organisierten Bekämpfung des Typhus, welche dieser Infektionskrankheit gegenüber zu so schönen und erfolgreichen Ergebnissen geführt hat, haben die bzgl. der Epidemiologie des Paratyphus und der Fleischvergiftungen gemachten Erfahrungen deutlich gelehrt, dass hier für die Verbreitung und Uebertragung der Krankheitskeime die Verhältnisse doch anders liegen und noch andere Wege in Betracht kommen, wie z. B. bei Typhus und Cholera, und dass ein Vorgehen, welches sich im wesentlichen und hauptsächlich nur gegen den infizierten Menschen richtet, bei der Bekämpfung der durch Paratyphus- und Gärtnerbakterien hervorgerufenen Krankheit nicht in gleicher Weise wie beim Typhus zum Ziele führt. Der Kampf wird vielmehr gegen diese Krankheiten erfolgreich nur durchgeführt werden können, wenn dabei die bei ihnen vorliegenden besonderen Verhältnisse darunter auch das Vorkommen dieser Bakterien in der Aussenwelt berücksichtigt werden.

Im Rahmen dieses Referates war es selbstverständlich nicht möglich, eine erschöpfende Darstellung des Gebietes zu geben und alle Autoren, die darüber gearbeitet haben, zu ihrem Rechte kommen zu lassen. In dieser Beziehung muss verwiesen werden auf die ausführlichen Darstellungen von Sacquépée,[2] Hübener,[3] und Sobernheim.[4]

[redacted]

V. Unter den Stämmen der Paratyphus- und der Gärtnergruppe, sowie unter den dem Bac. Paratyphi B und dem Bac. enteritidis Gärtner kulturell gleichen aber für deren Sera unempfindlichen Bakterien finden sich Kulturen, welche ähnlich wie der Bac. Glässer und der Bac. Voldagsen sowohl in ihrem kulturellen wie auch serologischen Verhalten Schwankungen und Veränderungen zeigen können.

VI. Von Paratyphus- und Gärtnerbazillen nicht unterscheidbare Bakterien sind im Darminhalt normaler Individuen verschiedener Tierarten, in den Organen gesunder Schlachttiere, in Wurst- und Fleischwaren, bei anderen Nahrungsmitteln, in Eis und Wasser sowie in den Entleerungen gesunder Menschen gefunden worden, bei welchen Beziehungen mit Paratyphus und Fleischvergiftungen nicht nachzuweisen waren. Es ist deshalb mit einer Verbreitung derartiger Bakterien in der Aussenwelt zu rechnen, deren Art und Stärke anscheinend von regionären Verschiedenheiten und vielleicht auch von zeitlichen Einflüssen abhängig sein kann.

[1] In einer neuerdings erschienenen Arbeit (Zeitschr. f. Hyg., Bd. 73, S. 75) kommt Bernhardt zu entsprechenden Ergebnissen.

[2] Bull. de l'Institut Pasteur, T. V, 1907, und T. VIII, 1910.

[3] Hübener, Fleischvergiftungen und Paratyphusinfektionen, Jena (Gustav Fischer), 1910, sowie Vierteljahrsschr. f. gerichtliche Medicin u. öffentliches Sanitätswesen, Bd. XLIII, 1912, Nr. 15 und 16.

[4] Hygienische Bundschau, Jahrg. XXII, 1912, Nr. 15 und 16.

ON THE ORGANISMS OF THE TYPHOID-COLON GROUP AND THEIR DIFFERENTIATION.[1]

Dr. J. Henderson Smith, Lister Institute, London.

I.

In the year 1906 M. Neisser recorded the occurrence of a coliform organism which, while primarily a nonfermenter of lactose, yet could give rise to a fermenting strain when grown on lactose agar. This organism was very carefully and thoroughly studied by Massini, who proved that the fermenting strain was not a contamination, but was really derived from the original nonfermenting organism and arose upon lactose agar as a variant with a new character which bred true. Since then numerous instances have been recorded by Burk, Jacobson, Revis, and others, and in particular by Twort and Reiner Müller, of members of the colon-typhoid group which displayed a similar capacity of varying toward one or more of the carbohydrates, and the fact of bacterial variation in this direction is now beyond dispute. The important bearing which this fact may have upon the differen-

tiation and identification of the pathogenic intestinal organisms is obvious, and for the last year or two W. J. Penfold has been carrying out in the Lister Institute a series of investigations on the subject. It is largely on his work that the following considerations are based.

If a broth or peptone-water culture of a normal typhoid bacillus be plated on the surface of a dulcite-agar plate, to which neutral red has been added, the colonies which develop after incubation are all without exception colorless. They do not produce enough free acid to change the color of the neutral red, and it is reasonable to suppose that they are composed, at least for the most part, of individuals which do not ferment the alcohol. When we continue to observe such a dulcite-agar plate, on which the colonies are discrete enough to allow of their free development, on a considerable number of the colonies papillae begin to appear, after a period which varies in different cases from 3 to 10 days. These papillae are small, very definite protuberances of characteristic appearance, somewhat irregular in shape, and of variable size. Their number, per colony, as also the number of colonies which show them, varies considerably, but the number, both of papillae and of papillated colonies, usually increases as time goes on. Eventually a proportion of the papillae turn red. On these plate cultures of typhoid, then, the organisms, which at first failed entirely to show any signs of fermenting dulcite, now do so, but only in certain limited parts of the total growth.

It might appear that what is occurring on the plates is that the organisms are turning to the dulcite as a source of food, having first exhausted the accessible supply of other constituents of the nutrient agar. In other words, that typhoid bacilli are capable of fermenting dulcite, but refuse to do so in the presence of other more appropriate nutriment. This is not the explanation of the late fermentation. If the organisms which compose such a papilla are plated out again upon dulcite agar, a number of the colonies which appear are red throughout, and these show no papillae. There is no longer an interval of several days, during which other food supply is being used up, but the fermentation begins early. The papilla then contains bacilli, which, unlike normal typhoid, are capable of attacking dulcite from the first. The papillated colony arose from a single organism of the original culture, and its progeny were at first, if not all, at all events preponderatingly nonfermenting. From among this progeny has arisen a strain, which now yields descendants preponderatingly fermenting. This new character is at first unstable, and after a short period of growth on normal media, the fermenting strain will again give progeny all or nearly all nonfermenting. But continued selection of colonies from dulcite agar or a few months' training on dulcite broth establishes the character, and a strain is obtained which

remains a dulcite fermenter, even after many months of cultivation in the absence of dulcite.

The sequence of events is perhaps more easily followed on plates, but a similar process takes place in dulcite broth. All, or nearly all, normal typhoid strains eventually turn a dulcite broth acid, but the time taken to do so is very variable, varying, in Penfold's strains, from 5 to 15 days. This time can readily be reduced by continued culture in dulcite broth to 3 days, and, eventually, to 1 day. By following the changes which occur in litmus dulcite peptone water, inoculated with normal typhoid, Penfold has shown the sequence of events leading up to the eventual acidity of the medium. Multiplication at first occurs, just as in peptone water containing none of the alcohol, and reaches the maximum of some 200,000,000 per 1 cubic centimeter, after which there is a slight decrease. During this period plating on dulcite agar shows that the organisms are non-fermenters. Then there develops a second rapid and very large increase in the number of organisms which may reach 600 to 1,000 millions per 1 cubic centimeter. This is entirely due to the development of dulcite-fermenting organisms, and the medium turns acid. The nonfermenting individuals almost completely disappear, and it appears almost as if the two strains are antagonistic to one another. If, as occurs in one type of culture, the numbers do not show this second great increase, the nonfermenters remain permanently in the majority. Fermenting individuals appear, but do not gain the upper hand, and the medium does not turn the full deep red of marked acidity.

So far as is known at present, growth on dulcite is the only means by which a dulcite fermenting strain can be obtained. This naturally suggests that the dulcite acts directly upon the individual typhoid bacillus in some specific manner, causing it to produce fermenting variants, which do not arise without this specific stimulus. This may eventually prove to be the correct view, but at present there is little to support it, and it is difficult to reconcile with some facts already known. If a nonfermenting individual be taken from a tube in which fermenting organisms have already arisen, it takes as long to produce a fermenting variant as an entirely untrained organism. It shows no indication of having been affected in any way by the dulcite, and there is nothing to suggest that it has been partially trained. The facts point rather to another interpretation which is sufficient to account for them without the hypothesis of specific alteration. It is enough to suppose that the normal typhoid bacillus, even growing on a broth medium without dulcite, tends to produce variants which have to a greater or less degree the power of fermenting the alcohol.

On a nondulcite medium there is nothing to encourage this type as compared with others, and as on its first appearance it does not breed true and occurs in very small numbers, the variant disappears again. But if there is dulcite present such organisms as are able to attack it receive a stimulus to their multiplication which the nonfermenters do not receive, and increasing to a disproportionate extent may eventually displace them entirely. The effect of the carbohydrate in the medium is to select one type of variant amongst those normally occurring rather than to induce the production of a quite new type. This increase of growth in the presence of an attackable carbohydrate is, as we have seen, what occurs in dulcite tubes when the fermenting variety appears, and it holds with other sugars also. A medium containing glucose, for example, supports and produces a larger population of typhoid than one which contains lactose or cane sugar, which the organism can not attack and in which the numbers are approximately the same as when no sugar is present. If the typhoid has been previously "trained" to attack lactose, then the numbers exceed the normal and approach those of the dulcite variant or glucose populations. The development of a protuberant papilla of itself indicates a greater energy of growth on the part of its components than that of the rest of the colony.

We have here, then, an instance of variability in the typhoid bacillus such that within a comparatively short time two races can be obtained differing from one another in the definite property of fermenting dulcite. Several other variations in the properties of typhoid with regard to carbohydrates are known. Reiner Müller has described the appearance of papillæ on isodulcite, and Penfold, like him, has found this appearance of papillæ to be a constant character of typhoid. If isodulcite plates are made from these papillæ, colonies are obtained which show no papillæ, and a race is obtained at once which breeds true and has lost the property of papilla formation upon isodulcite. An arabinose-fermenting strain is readily obtained, and strains are known which do and others which do not ferment glycerin. Special interest attaches to the lactose-fermenting variety produced by Twort. This organism was subsequently examined in detail by Penfold, and was found by him to be a genuine typhoid both in its lactose and nonlactose states, although it shows one or two slight divergencies from the perfectly typical *B. typhosus*. It took two years' constant growth on lactose before the variant could be obtained, and even now, after two years more on lactose, it does not breed true, showing a strong tendency to throw out atavists and revert to its nonfermenting state. After 18 months of training of a considerable number of strains on lactose media, Penfold has failed to produce another fermenting variety of *B. typhosus*, and it is evident that it is only with great difficulty and after a very long growth

on lactose that this particular variant can be produced from normal typhoid. Similar ill success has attended the attempt to produce variants by growth on a number of other media, such as adonite, erythrite, saccharose, amygdalin, salicin, and formates.

It appears, then, that *B. typhosus* is an organism which can be made to alter its character with regard to many of the carbohydrates. But it appears, also, that the readiness with which variation occurs differs in different cases. On the one hand we have the isodulcite-papilla variant, which arises very rapidly with every strain, and has the new character fixed immediately. As an intermediate comes the dulcite variant, which can be obtained from most strains fairly easily, and can be fixed comparatively quickly. On the other hand, we have the lactose-fermenting variant, which can be obtained only after years of "training" and has not yet been made to breed true. It may be that even those characters which have not yet been found to vary are really only characters whose variants take exceptionally long to arise, and that there is no single carbohydrate character which may not vary at one time or another under particular conditions. However that may be, the readiness with which the variant appears and the ease with which it becomes fixed show in general a rough agreement, and the more disposed an organism is to produce a particular variant the more readily is it disposed to take on the new character permanently.

It is probable that when other organisms have been examined in sufficient detail it will be found that they are like typhoid in this readiness to produce particular variants and reluctance to produce others. Unfortunately the data on this point are still somewhat meagre. The occurrence of variants has been described for many members of the typhoid-colon group among the pathogenic as well as the so-called nonpathogenic organisms occurring in the gut. Thus Reiner Müller has obtained papillæ with paratyphoid B on raffinose, and with Flexner's dysentery bacillus on isodulcite. Twort has induced the paratyphoids, and also Flexner and Shiga to ferment cane sugar, and Shiga has also been made to ferment lactose. Hiss so early as 1904 obtained a maltose-fermenting variant of bacillus Y, and other variations have been recorded. It is a pity that it is not always possible to ascertain from the published accounts how soon these alterations of character arose, nor whether the variants bred true, and in some cases the identity of the new strain with the old has not been very satisfactorily established. But it is clear that these variants show great differences in the readiness with which they arise. Massini's lactose-fermenting strain of *B. coli mutabile*, for example, arises at once and breeds true, while others require weeks or months of training on the particular sugar before a variant appears. More information is much needed on this point, for, so far as present

knowledge goes, it seems likely that along this line is to be found the theoretical justification of the recognized practical value of the carbohydrate tests.

It has been asserted that the possibility of variation is sufficient to destroy the value of the carbohydrate tests as aids to the differentiation and identification of the organisms of this group. If it is possible, so the argument runs, to make Shiga's dysentery bacillus ferment both lactose and cane sugar, we can not accept the absence of these properties as significant characteristics of the organism. If plates made from a suspected water or feces from a case of enteritis show only lactose-fermenting colonies, we can never be sure that these colonies, or some of them, are not really colonies of a typhoid variant. May not something of this kind be the real explanation of the extreme difficulty of isolating typhoid from water?

The difficulty must be admitted and the possibility recognized that so far as carbohydrate tests go, one organism may be convertible into another. We can, in fact, conceive the possibility of an organism with the sugar reactions of a *B. coli* and the agglutinating and other properties of a dysentery bacillus, including its pathogenicity. It may even be the case that in certain instances something of this sort does actually occur in nature.

Penfold has brought forward some evidence to show that, parallel to the main group of lactose-fermenting organisms in the intestine, there are corresponding groups of nonlactise-fermenting bacteria, occurring naturally in fair numbers, which belong to the mutabile class and are convertible into the fermenting types, and he considers that one group may arise from its corresponding group under natural conditions. Even if this were proved, however, beyond dispute, it would not discredit the usefulness of the carbohydrate tests. It only shows us that there are certain organisms for which the lactose relation is unsuitable as a group character; it does not touch the possibility that there are other carbohydrates more suitable. These particular organisms of the mutabile group have a pronounced tendency to vary toward lactose, and this experience in the laboratory would lead us to anticipate the occurrence of such variants in nature. In a similar way, we know that typhoid has a pronounced tendency to vary toward glycerin, and this laboratory experience would lead us to reject glycerin fermentation as a safe character of the typhoid group.[2] The dulcite-fermenting variety is less likely to arise naturally, but even this is a frequently occurring variation with a tendency to breed true. We should prefer to take, as a type character, one toward which a variant arises only with great difficulty and breeds true only in very exceptional circumstances existing over a long period, such as the lactose relation. Lactose, therefore, is a suitable sugar in the case of typhoid, but unsuitable in the case of

B. coli mutabile. Further experience will show for the different groups of organisms what are the carbohydrates on which reliance is to be placed as distinctive media.

To some extent this knowledge has been already acquired. It is usual to make the carbohydrate tests in fluid media with an incubation of several days, say, from 3 to 7 days. A variant which does not arise in that time is probably not a very common variant, and so in practice our tests indicate approximately the lines along which further knowledge will be found to develop. The discrepancies which different observers occasionally record in the reactions of organisms (e. g., the typhoid relation to dulcite and the different behavior on solid and fluid media) find their explanation in this occurrence of variations.

It is not claimed by the supporters of the carbohydrate reactions that they are capable of giving a complete and systematic classification even of the intestinal bacteria according to their biological relationships. We have at present no means of doing this with certainty. It must be remembered that most bacteria are extremely variable in other characters as well as in their sugar reactions. In pigment production, toxin production, gelatin liquefaction, and in practically all cultural reactions, variability is very frequent. Variations of virulence are amongst the oldest and commonest observations of bacteriology. Even agglutinability is not a constant character, as the frequent occurrence of strains nonagglutinating at the time of isolation from the body is sufficient to prove. In many of these instances the variation consists simply of the gain or loss of a definite property found only with the particular species, and not in the acquirement of a character possessed by another and different species, and in this respect such changes may appear to differ fundamentally from the carbohydrate changes. (This may be not a very real distinction, since the carbohydrate reactions are none of them specific under natural conditions in the way in which, say, the toxin production of diphtheria is specific, but each is common to many species.)

Such instances show that variability is one of the characteristic properties of bacterial protoplasm, and that systematic classification is likely to prove exceedingly complex. The carbohydrates do in large measure supply a simple method of practical differentiation of proved value, and it is the only method at present available which is sufficiently elastic to cover a large number of different organisms. That it does in some instances group together organisms with close pathological relationship is undeniable, and there would seem to be no reason to doubt that as a general rule closely allied strains will produce similar ferments.

It has been suggested by Reiner Müller that variability in certain directions may be actually specific for certain organisms, and he

instances the case of typhoid, of which all strains give the isodulcite variation. This may be a usual or practically constant character of typhoid, but, as he himself recognizes, it belongs to other organisms also, and there is no known variation which is quite specific in the sense that it is given by every member of a species, and by no others. A tendency to variation in one particular direction may, indeed, be on occasion a useful aid in differentiating closely similar bacteria. R. Müller found that paratyphoid B. produces papillæ on raffinose, while *B. Aertryck* does not. It is usual, on the continent of Europe, to consider these organisms as strictly identical. Boycott, Bainbridge, and others in England hold that they are distinct—separable by means of agglutinin-absorption tests—and it is an interesting confirmation of this view that Penfold, using the raffinose test, was able to separate a considerable number of strains into two groups, which practically coincided with the groups distinguished by Bainbridge in using the absorption method.

In the variations we have been discussing the new strain differs from its parent in a single character; alteration in one character does not necessarily involve alteration in another. Two or more such variations may be superadded, but several characters do not vary simultaneously. Since the fermentation of the different carbohydrates is presumably due to the action of different ferments, and since we have no reason to suppose that power on the part of an organism to produce any one ferment entails either the capacity or incapacity to produce any other ferment, there does not appear to be at present any ground for anticipating that such concomitant variations will often be found to occur. Penfold's experiments on gas production, however, show that loss of a single ferment may affect several reactions.[3] By growing various organisms on chloracetic acid agar and selecting colonies from the plates, Penfold succeeded, in a number of instances, in suppressing the formation of gas from sugars, although power to produce acid remained unimpaired. By this means he has bred strains of *B. enteritidis Gaertner*, *B. paratyphosus B*, *B. Grünthal*, and *B. coli Escherich* (*B. acidi lactici* and some others remain refractory), which no longer produce gas from glucose. With the loss of this power went the loss of the gas production from various other carbohydrates.

The extent of this loss differs a little in the case of different organisms, but, speaking generally, it was found that if an organism failed to produce gas from a hexose or pentose which it was able to attack, then it also failed to produce gas from other fermentable hexoses or pentoses, but might continue to produce gas from such alcohols as it was able to attack. The obvious interpretation of this phenomenon is that similar sugars yield as the result of fermentation

similar products, which are attackable by a single ferment, but that alcohols yield different products requiring other ferments for their further decomposition. This work of Penfold has another interest, in that the altered strains are apparently also the strains which show exceptional powers of resistance to the monochloracetic acid, but the possible significance of this observation can not yet be fully estimated.

II.

It is usual to divide the bacilli of the colon-typhoid group into two main subdivisions according as they do or do not ferment lactose. This practice has the sanction of a very large experience, but it must be remembered that the nonlactose fermenters include one group of organisms (that of the *B. Coli mutabile*), which are really more closely allied to the lactose fermenters. These organisms, which are more common than Massini's experience led him to believe, have a pronounced tendency to produce fermenting variants, and in fluid media most of them eventually ferment lactose, though they do so only late, rarely before the sixth day of growth. If the existence of this group is kept in mind, little practical inconvenience is caused, and the classification by lactose has the advantage of bringing together the more definitely pathogenic organisms of the intestine hitherto recognized, and is not invalidated by the facts of variation, so far as they are yet known. None of the organisms of this division, to which most importance is attached in human pathology, shows any marked tendency to produce lactose-fermenting strains, and in laboratory experience it is only by very long training that the occurrence of fermenting variants can be demonstrated. Further, various workers who have had large experience in this field have the impression that nonlactose fermenters are in some way associated with abnormal conditions of the gut. They occur of course in the normal intestine, but in diarrheal or local inflammatory conditions they appear to increase in numbers relatively to the lactose fermenters. One may recall, in this connection, the enormous predominance of typhoid and dysentery bacilli which is frequently met with in the stools of carriers or patients suffering from these diseases.

When the group of late fermenters and the gelatin liquefiers have been separated out there remains a large number of nonlactose bacilli, and among these one can distinguish, by cultural methods alone, three main groups, about which something requires to be said. These three groups are the typhoid, paratyphoid Gaertner or enteritis, and the dysentry group, and around these may be collected a large number of organisms, which more or less resemble them. There remain still a number of bacilli, which may be simi-

larly brought together into groupings of allied members. It is quite probable that some of them have definite pathological importance, but this has not yet been clearly established for any of them. These have been very carefully studied by H. de R. Morgan, who over a series of years examined the intestinal bacilli which neither ferment lactose nor liquefy gelatin. His investigations were concerned chiefly with summer diarrhea, cholera infantum (where he found a remarkable association of this disease with one particular organism rarely occurring elsewhere, and now widely known as Morgan's No. 1), but they included also the intestinal flora of children, adults, and animals, both in the normal state and in other abnormal conditions, accompanied by diarrhea or enteritis. The detailed account of these organisms is to be found in his papers, and a considerable mass of confirmatory and additional information has been accumulated by other workers in cognate and more specialized fields of research.

The typhoid group.—The typhoid group requires only a brief reference. The characters of the typhoid bacillus are well known, and I need only recall here that it produces acid without gas from glucose, mannite, and sorbite, turns milk acid without clotting it, and does not ferment dulcite, saccharose, nor, of course, lactose, and does not produce indol nor liquefy gelatin. These characters are constant for all naturally occurring strains of typhoid, with the possible exception of dulcite, already discussed. The *B. typhosus* is, in fact, a remarkably well-defined and stable organism. Very many strains have been examined in a series of carbohydrates much larger than the above without the detection of differences. An exception may be found in glycerin, since both fermenting and nonfermenting strains have been described, and it is probable that glycerin resembles dulcite or isodulcite in being a substance to which variants are readily produced. But it seems beyond doubt that unless artificial means are taken to alter it, the typhoid bacillus is very constant in its cultural characters. All these strains, moreover, agree in their serological characters, and there is rarely any difficulty in identifying *B. typhosus* when it is met. Further, it is an organism to which close allies, as judged by the cultural reactions, do not occur naturally. (A somewhat similar bacillus has been found by Ledingham to occur frequently in flies, but it produces indol, produces alkali in milk, and does not ferment sorbite.)

Nonmotile strains have been described, and strains inagglutinable on first isolation are comparatively frequent. If we accept, as most would, motility and agglutinability as definite characters of the *B. typhosus*, such strains must be accepted as subvariants, and they illustrate the necessity of employing more than one criterion in identifying any organism. No one would refuse to accept as typhoid an organism which, otherwise typical, is at first inagglutinable, but sub-

sequently conforms to type after a short period of laboratory culture. But the duration of inagglutinability in actually observed cases is very variable and may extend to several subcultures. Moreover, other organisms, notably Gaertner's bacillus and paratyphosus B., are occasionally no less strongly agglutinated by typhoid sera than a true *B. typhosus*. Neither the presence nor the absence of the agglutination character is in itself finally conclusive, and we must recognize that agglutinability is also a variable characteristic. In the case of typhoid, the stability of the cultural reactions and the nonoccurrence of organisms which closely resemble it make these reactions of especial value in the differentiation.

The enteritis or Gaertner-paratyphoid group.—The second group is the enteritis or Gaertner-paratyphoid group, of which culturally the type member is the *B. Gaertner*. Its chief cultural characters which are the same as those of *paratyphosus B.* and *B. suipestifer*, are the following: It produces acid with gas from glucose, mannite, dulcite, and sorbite, does not ferment cane sugar nor lactose, does not produce indol nor liquefy gelatin, and litmus milk is at first made acid, but from about the third day on the milk turns alkaline and by the seventh day becomes strongly alkaline, without at any time clot formation or digestion. Certain other reactions will be referred to immediately. This group has been the subject of much confusion and is still the cause of a good deal of controversy. To some extent this is a relic of the preagglutination days, but to a still greater degree it is due to a loose application of the term "paratyphoid" to imperfectly examined organisms.

The cultural characters which we have detailed mark off a definite group of bacilli within which further distinction can be made by other methods, as will presently be described. But there occur in the normal intestine several organisms which are culturally very much like the type organisms of the enteritis group, but are to be definitely distinguished from them. Of these there are at least two main subgroups, one of which ferments cane sugar and one which does not ferment dulcite. Both are comparatively common, and neither has any claim to the name of paratyphoid. Bainbridge and O'Brien examined a number of strains of the saccharose fermenters, which had been isolated by Ledingham, and while they found minor variations in the cultural reactions they obtained no significant agglutination of any of them with Gaertner, paratyphoid B., or other sera made from organisms of the enteritis group. In this their experience agrees with that of Savage and of Morgan, who also found the same to be true of the dulcite nonfermenters. The members of both these subgroups are apparently quite distinct from the genuine enteritis organisms. Unfortunately, however, many workers, especially on the Continent, adopt even at the present time criteria

which do not exclude these bacteria, and by omitting dulcite, sometimes even saccharose, from their tests they extend the name of paratyphoid to organisms which certainly should not receive it. This has led to confusion in at least two directions. On the one hand the epidemiology of paratyphoid fever is obscured by their inclusion in this group, and, on the other, the agglutination test is discredited because so many so-called paratyphoid strains fail to give it.

The organisms of these two subgroups, the cane-sugar fermenters and dulcite nonfermenters, are not known to have any pathogenic significance for man, but the pathogenic B. paratyphosus A. bears a close resemblance culturally to the type organisms. Paratyphoid A. differs from the latter only in not producing enough alkali in litmus milk to overcome again the initial acidity it causes. The milk turns acid and remains so permanently without formation of clot or true digestion. This organism can be readily identified by agglutination as well as by the milk reaction. It is not common in Europe, but in India it is frequently met with, and is a common cause there of so-called paratyphoid fever. It is not yet known whether subvarieties of this organism might be distinguished by means of agglutination or other methods, but it may be noted that Morgan has isolated an organism identical in all respects with paratyphoid A., except that it was not agglutinated by a strong paratyphoid A. serum.

There is still one other group of organisms which can be distinguished from the true type organisms by cultural tests, if we extend them a little further. The type bacilli ferment galactose, arabinose, and maltose, but produce no apparent change in salicin, raffinose, or inulin. In the intestine of healthy animals occurs an organism which, resembling the type in other cultural respects, differs from it in fermenting salicin. It is fairly frequent; e. g., Savage found it eight times in the examination of 31 animals, and its differentiation is confirmed by the absence of pathogenicity and of agglutination with standard sera.

When the field has been narrowed by the exclusion of these three subgroups, there remains the mass of organisms, which are culturally indistinguishable from the types. As was first shown by Durham and de Nobele, these are separable into two very definite subgroups by agglutination reactions. First comes *B. Gaertner*, an organism sharply and readily differentiated by means of agglutination, since it is not affected to any significant extent by sera of other members of the group. The fact that it may be agglutinated by some typhoid sera, and that, conversely, typhoid bacilli may be agglutinated by Gaertner sera, causes no difficulty in identification, because of the other characteristics of these organisms. *B. Gaertner* is the organism responsible for many attacks of food-poisoning, and

it is contained in many rat viruses including *B. danysz*. It is believed to have caused, and is certainly associated with, spontaneous outbreaks of disease in mice, guinea pigs (Bainbridge and O'Brien, MacConkey), and rats (Boycott), and there is some evidence that it is a normal inhabitant of rats and mice, or, at all events, is apt to develop in these animals when they suffer from depressing or toxic influences. What are the conditions which bring about the sudden epizootic virulence of the organism are unknown, but it is of interest to note that, in a similar epizootic in guinea pigs, associated with *B. suipestifer*, Petrie and O'Brien found reason to believe in the occurrence of a filter-passing virus. In a rat epizootic, Boycott isolated an organism identical with *B. Gaertner* in all respects, cultural, and serological (including absorption tests), which possessed the property of changing the haemoglobin in infected animals into methaemoglobin, so that their blood was chocolate or brown in color during life.

The second subgroup, into which serum reactions divide the culturally typical organisms, in its turn comprises two members, the *B. paratyphosus B.* and the *B. suipestifer* (with the latter of which authorities are agreed that *B. Aertryck* is identical). Both organisms are agglutinated by the same sera, and to approximately equal degree in most cases. Many authorities maintain that there is no real ground for drawing any distinction between them. Most of the English workers, however, and some German writers believe that they are separable from one another by absorption tests carefully carried out, and that they are definitely distinct organisms. Bainbridge and O'Brien, the most recent English investigators to make an extended study of the subject, examined by this test a large number of strains from various sources, and they found that they fell into two groups which corresponded, on the one hand, to the *B. paratyphosus B.* associated with paratyphoid infection in man, and on the other to *B suipestifer*, associated with food poisoning. Their results are so consistent and clear that it is difficult to believe the distinction to be unreal. It has further received support from Penfold's application to their strains of the raffinose-papilla test already described, and also from complement-deviation experiments of H. R. Dean.

The culturally typical organisms of the enteritis group then are divisible into three subgroups, *B. Gaertner*, *paratyphosus B.*, and *B. suipestifer* (or *Aertryck*), and into one or other of these groups fall all or nearly all the organisms associated with food-poisoning outbreaks recorded in many places since Gaertner's original description, as well as many of the organisms associated with animal epizootics. It may be noted here that the *B. typhi murium* is apparently not a

separate species, but, of the organisms passing under that name, some are *B. Gaertner* and some are *B. suipestifer*.

It is outside the scope of this paper to discuss the epidemiology of the diseases caused by these organisms, but it may be permissible to draw attention to the importance of always distinguishing them clearly. As a single illustration, it is sufficient to mention the suggestion, which their results led Bainbridge and O'Brien to put forward, that *B. suipestifer* and *B. paratyphosus B.* have a different distribution in nature, the former occurring in the intestine of pigs and other animals, the latter in the human alimentary tract.

The dysentery group.—Some authorities, such as Lentz, maintain that the dysentery organisms do not really belong to the typhoid-colon group. Practically, however, they must be included, since they have to be distinguished from other intestinal bacteria which they closely resemble. In some respects they are the least satisfactory of the groups with which we have to deal, as in them we meet with a marked difference in grouping according as we take the cultural or the agglutination characters for our differentiating tests.

One of the varieties may be dismissed quite briefly, viz, the original *B. dysenteriæ* of Shiga. This organism, which is nonmotile, ferments glucose without production of gas, and, after preliminary acidification, turns milk alkaline on or soon after the third day. It does not ferment mannite, dulcite, cane sugar, lactose, nor sorbite, and does not produce indol. A somewhat similar organism has been described by Morgan, but it is motile and produces indol, and the agglutination reactions of the Shiga bacillus are characteristic.

It is when we come to the mannite-fermenting types of dysentery bacilli that difficulties arise. Some doubt has been expressed as to their claim to be considered genuine dysentery bacilli at all, owing to an alleged milder clinical course of the disease with which they are associated, but they frequently produce extremely severe or fatal dysentery, and a doubt of this kind is unjustified. An individual position is taken amongst them by the bacillus of Strong. This organism is unlike the rest in fermenting dulcite and cane sugar and in producing clot in milk, and its agglutination reactions also separate it from the others. As it has apparently been only once found in association with dysentery, it is of subordinate importance, but we may notice that organisms not very dissimilar culturally and agglutinated by Strong serum have been found by Morgan to occur in the stools of typhoid convalescents.

The representative organism of the mannite-fermenting type is Flexner's *B. dysenteriæ*, and it is the best known member of a group which possesses the following general characters: They are nonmotile, ferment glucose and mannite without production of gas, turn milk

alkaline after preliminary acidification, produce indol, and do not ferment lactose, dulcite, or cane sugar, and do not liquefy gelatin. These group characters are possessed by most of the mannite-fermenting dysentery organisms, though variations occur in the readiness with which they produce alkali in milk and form indol. Whether all intestinal organisms with these characters are potential producers of dysentery can not be definitely stated as yet. It seems improbable, since they occur not infrequently in individuals with no history of dysentery, but sufficient evidence on the point is lacking. It is apparently questionable whether agglutinability by Shiga, Strong, Flexner, or even by Y., serum is a necessary property of all the pathogenic members of the group.

Flexner's organism ferments maltose and dextrin, and does not ferment sorbite, but other members of the subgroup show differences in one or more of these characters. This has recently been clearly shown by Morgan, who examined the behavior toward 18 carbohydrates of over 50 strains, and it has also been brought out by Tebbutt in his study of institutional dysentery in England, as well as by others. The best known of these, the Y. bacillus of Hiss and Russell, does not ferment maltose in its original state, and this sugar has therefore been used as a basis of subclassification. We know, however, from Hiss's own work that the Y. organism readily acquires the power of fermenting maltose, and there are other grounds for doubting the stability of the character. Bacillus Y. resembles B. Flexner much more closely than do some other undeniable dysentery strains, e. g., some of the El Tor organisms of Ruffer and Willmore; and a primary subdivision on a maltose basis, even if the character were less variable than we know it to be, would separate Y. and Flexner, while bringing together other organisms much less closely alike. It would appear to be more satisfactory to adopt a subdivision according to the more stable sorbite character, as suggested by Tebbutt, and to redivide the subgroups, so formed, into those which do and those which do not ferment dextrin. This gives us four groups, each of which contains some dysentery organisms. It brings the Y. bacillus into the same subgroup with the true Flexner, from which it can, if desired, be distinguished by the maltose test.

By no system of classification, however, can we bring the cultural and serological reactions into harmony. It appears that motile bacilli with claims, on cultural grounds, to admission to the group, are definitely not agglutinated by dysentery sera, but, otherwise, the results are quite discordant. All observers are agreed that absorption methods are unsatisfactory for these organisms, and in every subgroup there occur ome strains which are agglutinable by Flexner

serum and some which are not. We must recognize the fact that the biochemical and serum reactions are not at one in this group. Of course there is really no *a priori* ground for expecting them to agree, since variation in one character is not necessarily accomplished by variation in another. Between the two conflicting methods of classification, we have no conclusive reason for preferring the one to the other, and we must wait for further experience on the subject. The impression one gains is that the dysentery organisms, as a group, are in a very unstable condition, and have not acquired fixed characters such as we find in other bacilli of the typhoid-colon class. A thorough examination of representative members, from the mutation or variation point of view, is much to be desired.

The details which have been given in the preceding pages of this section enable us accurately and easily to subdivide such of the organisms of the typhoid-colon group as do not ferment lactose and do not liquefy gelatin into a number of distinct subgroups. The members of each subgroup resemble each other more or less closely, but they admit of a further subdivision by methods which are in most cases readily practicable. The resulting classification is summarized briefly in the following table:

TABLE OF ORGANISMS WHICH NEITHER FERMENT LACTOSE NOR LIQUEFY GELATIN.

I. Late lactose fermenters.
II. Certain groups of no known pathogenic importance.
III. Typhoid group.
IV. Paratyphoid-enteritis group:
  1. Atypical members:
    (*a*) Saccharose fermenters.
    (*b*) Dulcite nonfermenters.
    (*c*) *B. paratyphosus A.*
    (*d*) Salicin fermenters.
  2. Typical members:
    (*a*) *B. enteriditis Gaertner* distinguished from (*b*) and (*c*) by agglutination.
    (*b*) *B. paratyphosus B.*, distinguished from (*c*) by absorption.
    (*c*) *B. suipestifer.*
V. Dysentery group:
  1. Mannite nonfermenting. *B. dysenteriae Shiga.*
  2. Mannite fermenting:
    (*a*) *B. dysenteriae Strong.*
    (*b*) Sorbite fermenters.
      (i) Dextrin nonfermenting.
      (ii) Dextrin fermenting.
    (*c*) Sorbite nonfermenters.
      (i) Dextrin nonfermenting.
      (ii) Dextrin fermenting.
        (a) Maltose fermenting (*B. dysenteriae Flexner*).
        (b) Maltose nonfermenting (*B. dysenteriae Y*).

III.

In conclusion, there are one or two general considerations which I wish to bring forward. The amount of work which is done in connection with the typhoid-colon group every year, and in all parts of the world, is simply enormous. Even if we omit the routine examinations of such material as water, the work devoted to the investigation of fæces alone in connection with carriers, food poisonings, enteritis cases, genuine or suspected, and so on, is immense. This represents a large expenditure of energy, and, unfortunately, much of it does less than it might to advance our knowledge of bacteriology and the epidemiology of intestinal disease. There is a waste of energy in two directions. On the one hand, much time and labor are in many cases expended on the elaboration of points which contribute little or nothing to establishing the identity of the organism studied, and, on the other, much of what is considered by many to be essential to its complete description is too often omitted.

The early bacteriologists, for want of other diagnostic tests, were compelled to lay stress on the appearance of colonies on the ordinary media, their vine-leaf shape, prominence, moistness, translucency, and so on. Such points as these are of almost no value as differential tests. Even a blue colony on Conradi-Drigalski is of only elementary differential value, and the appearance of such colonies, their exact shade of blueness, etc., does not take the distinction beyond the primary division into lactose fermenters and nonlactose fermenters. But we still quite frequently find these details set out with laborious minuteness as if they contributed essential information in the distinction of the group members from one another. Lengthy descriptions of this kind do not repay the trouble they demand, and will no doubt gradually disappear in time; but we are threatened with another cause of waste of energy in the multiplication of tests. The introduction of new tests is most desirable, for by them we may hope to deepen our knowledge, but when a test has received an extensive trial and has contributed nothing fresh to our knowledge, it should be dropped again. There are certain complicated media, for example, in frequent use for the growth of typhoid bacilli which might very well lapse into disuse.

On the other hand, I would urge a more general recognition of the value of the carbohydrate media. These tests supply most valuable help in the differentiation of the typhoidlike bacteria from one another. This is true of all the subgroups, but they are especially important in the case of the Gaertner-paratyphoid group, where we meet so many organisms closely resembling the genuine pathogenic bacilli. Yet we find bacteriologists, even of great and deserved repute, classifying organisms whose dulcite or saccharose reactions have not been

studied as identical in fermentation activity with paratyphoid B. Possibly they look on these points as of minor importance, but the want of information of this kind greatly reduces the value to others of the work done, and handicaps them in subsequent investigations on similar lines.

This is an excellent illustration of what really constitutes at present a great part of the difficulty which these organisms present, viz, the lack of uniformity in the methods by which they are studied. Bacteriologists in different countries, and in different parts of the same country, rely on different criteria in establishing a diagnosis, and, as a consequence, neglect the tests in which they happen to place less faith.

To some extent this is inevitable, but it has the result of making the information collected by the followers of one set of criteria inadequate and therefore largely useless to those who adopt another set. Now, taken altogether, the number of tests employed by the leading bacteriologists who have devoted much time to the study of these intestinal bacilli is not very large, and it should be possible for all workers to adopt as a basis a uniform standard of minimum requirements. This standard would not be exhaustive in the sense of including all known tests, and individual workers would naturally add other tests, either old or new, to which they attached importance. It need have nothing dogmatic about it, and would not commit those who adopted it to a belief in the validity of all the tests it included, and it would be subject to revision from time to time. But it would be comprehensive enough to cover all the most important tests on which bacteriologists of different schools are accustomed to rely. It would, therefore, insure that work done in one part of the world by one school would be available to other schools elsewhere, and we should avoid the very real present difficulty, that the work of any one school is of full value only to that school and to no other. Something of this kind seems very much to be desired. Naturally, it could be drawn up only by an association, at which the different methods of examination were adequately represented. If this section of the International Congress of Hygiene and Demography were to appoint a representative committee to draft recommendations of the nature indicated it would take a step which it is well qualified to take and one which would be of great value to all bacteriologists.

RÉSUMÉ.

It is scarcely possible to summarize this paper briefly, but its scope may be indicated by the following:

Mutation or variation, as it occurs in members of the typhoid-colon group, is discussed in some detail, and it is pointed out that,

while many members of the group are capable of such alteration toward one or more carbohydrates, this does not occur haphazard but in certain directions which are definite for each organism. An organism produces with greater readiness variants toward some carbohydrates than to others, and the more disposed an organism is to produce a particular variant, the more readily does it take the new character permanently. Variability is one of the characteristics of bacteria, and affects most of their known properties, and the fact that variation occurs toward carbohydrates does not invalidate their use as aids to differentiation. The carbohydrate media are the most elastic, most practical, and most satisfactory means at present available of distinguishing the members of this group.

The primary division being made into those which do and those which do not ferment lactose, the nonlactose fermenters, which include the important pathogenic members, are considered in detail. The three prominent groups of typhoid, paratyphoid, Gaertner, and dysentery, are taken separately, and their characters, and those of the organisms most closely resembling them, are set out. Finally, a plea is put forward for greater uniformity, and, if possible, some standardization of the methods employed in their study.

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Twort, Proc. Roy. Soc., 1907, Series B, vol. 79, p. 329.

[1]At the Berlin meeting of this Congress, in 1907, certain institutes were requested to undertake an inquiry into the differentiation of the "typhoidlike" bacteria, and to present a report upon these organisms at the Washington meeting this year. This paper constitutes the report of the Lister Institute of Preventive Medicine, London.

[2]The converse is not necessarily true, however, since all strains of typhoid produce papillæ on isodulcite, but lose this character readily, and no strain has yet been isolated which is already in the nonpapilla-forming state.

[3]With this may be compared the nongas-producing *B. Aertryck* recorded by Bainbridge.

SUR LES SALMONELLOSES (BACILLES PARATYPHIQUES B, BACILLES DES EMPOISONNEMENTS ALIMENTAIRES, ETC.).

M. le Dr. SACQUEPÉE, Professeur au Val-de-Grâce, Paris, France.

I. GÉNÉRALITÉS.

Sous la désignation commune de bacilles paratyphiques, on s'est accoutumé et on continue à comprendre des espèces microbiennes certainement différentes.

À tous points de vue, le bacille paratyphique A et le bacille paratyphique B doivent être séparés l'un de l'autre.

Nous nous occuperons exclusivement du bacille paratyphique B et des espèces, ou très voisines, ou identiques.

À l'ensemble de ces espèces, nous avons déjà donné le nom de Salmonelloses, du nom de Salmon, qui a décrit, sous le nom de bacille du hog cholera, le premier représentant du groupe.

1°. Les caractères culturaux et morphologiques, communs à tous les Salmonelloses, sont connus, et il nous paraît inutile à y insister.

2°. Les réactions biologiques (propriétés des sérums) divisent le groupe des Salmonelloses en deux sous-groups:

a. Sous-groupe I. Comprenant comme type le plus important le bacille d'empoisonnements alimentaires (ou bacille carné) de Gärtner.

b. Sous-groupe II. Numériquement beaucoup plus répandu, comprenant entre autres: Le bacille carné du type aertrycke; le bacille paratyphique B des infections par typhoïdes humaines; le bacille de la psittacose; le virus Loeffler; quelques échantillons de hog cholera (échantillons Salmon).

D'une manière générale, le sérum spécifique pour le sous groupe I. présente une agglutinine et une sensibilisatrice spécifiques pour tous les représentants du sous groupe I; ces mêmes sérums n'ont pas d'action bien nette sur le bacille du sous groupe II.

Inversement, les sérums spécifiques pour l'une quelconque des espèces du sous groupe II présentent une agglutinine et une sensi-

bilisatrice spécifiques pour tous les représentants du sous groupe II. Le degré d'activité des sérums peut être un peu variable suivant les espèces, sans que cette inégalité d'action permette de les séparer nettement les unes des autres.

L'épreuve de la saturation ne les sépare pas davantage.

Les sérums du sous groupe II ne manifestent aucune action spécifique à l'égard des bacilles du sous groupe I.

3°. Les caractères culturaux et morphologiques des salmonelloses ne sont pas à eux seuls suffisants pour la délimitation du groupe; tous, sans exception, y comprit le caméléonage du lait et du petit lait tournesolés, peuvent appartenir à des variétés de paracolibacilles, ne hog cholera avec les Salmonelloses.

Appartiennent exclusivement à ce groupe, les microbes qui présentent, outre les caractères morphologique et culturaux indispensables, la propriété d'être agglutinés à dose convenable ou de provoquer la déviation du complément en présence de l'un ou l'autre des deux sérums spécifiques signalés plus haut.

4°. On a discuté et on discute encore sur la parenté des bacilles du hog choléra avec les Salmonelloses.

En fait, il paraî établi que les bacilles dits du hog choléra ne constituent pas l'agent spécifique de cette maladie; ils ne représentent que des infections secondaires. Comme tels, on conçoit qu'ils puissent ne pas constituer une espèce, mais bien un groupement hétérogène de microbes variés.

Seule appartient à notre cadre la variété décrite originellement par Salmon.

II. RÉPARTITION.

L'expansion des Salmonelloses est considérable.

1°. Chez l'homme, à l'état pathologique, dans deux séries de circonstances cliniquement différentes.

(*a*) Au cours des infections paratyphoïdes, ces microbes peuvent être décelés dans le sang, dans la plupart des organes, dans les excréta (selles, urines).

Ils peuvent persister dans les selles pendant quelque temps après la guérison.

(*b*) Au cours des empoisonnements alimentaires; les Salmonelloses existent, généralement en grande quantité, dans le contenu intestinal, dans le contenu gastrique; elles ne passent dans le sang que chez les sujets atteints de formes extrêmement graves.

2. *Chez les animaux malades.*—(*a*) Chez les animaux boucherie, susceptibles de présenter pendant la vie des lésions extrèmement variées. Diarrhée infectieuse, phlébite ombilicale, pyohémie, chez le veau; diarrhée, métrite, chez la vache; abcès, chez le porc; abcès, entérite, chez le cheval.

(*b*) Au cours d'épizootie chez les rongeurs, rats, souris, cobayes, etc. * * *

3. Dans les aliments contaminés les plus divers: viande, légumes, poisson, crêmes de patisserie, etc.

4. Exceptionnellement, on peut rencontrer les mêmes microbes, en dehors de tout état pathologique appréciable, soit chez l'homme, soit chez diverses espèces animales, spécialement les animaux de boucherie.

II. SALMONELLOSES DANS LES ALIMENTS ANAMAUX.

Nous devons insister spécialement sur la bactériologie des aliments animaux.

Les aliments animaux susceptibles de nous intéresser sont: la viande et le lait.

(A) *Viandes.*—On peut rencontrer des Salmonelloses dans deux circonstances différentes:

Dans la viande provenant d'animaux infectés (viande malade).

Dans la viande qui, provenant d'animaux sains, a été contaminée après abattage (viandes contaminées).

1°. *Viandes malades.*—Comme il a été dit ci-dessus, il est établi que certaines affections des animaux de boucherie sont provoqués par des Salmonelloses, spécialement chez le veau, la vache, le bœuf, le porc, le cheval.

En pareil cas, les microbes se rencontrent, non seulement dans les lésions locales, mais encore dans tous les organes et dans la chair musculaire. Il s'agit en réalité d'une septicémie. Cette dernière se manifeste parfois par une pullulation des microbes à l'intérieur même des vaisseaux.

La viande et les viscères de ces animaux, inférés par l'homme, provoquant chez lui des empoisonnements alimentaires.

Il convient en outre de noter:

(*a*) Que, sous certaines observations, l'examen après abattage n'a permié de déceler aucune lésion appréciable, bien que l'animal fût certainement infecté, la viande renfermant des Salmonelloses et ayant provoqué des accidents toxiques.

Le fait n'a rien de surprenant pour des microbes à cet ordre, qui sont aptes autant que nul autre à provoquer des septicémies, sans lésion grossière apparente, à l'instant des infections paratyphoïdes humaines. En pareil cas, on ne pourrait être appelé à soupçonner un état pathologique qu'en soumettant l'animal à une observation sanitaire pendant quelque temps avant l'abattage;

(*b*) Que la chair musculaire des animaux infectés peut ne présenter aucune altération appréciable;

(*c*) Que la cuisson diminue généralement la toxicité des viandes infectés, sans toutefois la faire disparaître complètement.

(*d*) Que certaines espèces animales, spécialement le mouton, sont très rarement infectés par les Salmonelloses.

Il semble ressortir de certaines recherches, qui d'ailleurs attendent confirmation, qu'on pourrait trouver exceptionnellement des Salmonelloses dans la viande saine provenant d'animaux sains, surtout quand ces derniers ont été surmenés avant l'abattage. Le fait n'a rien d'impossible, car il est connu qu'à la faveur de toute diminution de la résistance de l'organisme les microbes préexistants dans l'intestin peuvent émigrer dans la circulation générale.

De semblables constatations intéressent plus la biologie générale que l'hygiène; car il est vraisemblable que ces quelques microbes éparés dans les tissus peu ou pas altérés n'y rencontrent que des conditions défavorables à leur développement ou même à leur simple persistance. Expérimentalement, les septicémies que nous avons provoquées dans des conditions très analogues se sont toujours montrées éphémères et bénignes.

2°. *Viandes contaminées.*—Une viande, primitivement saine, peut se trouver contaminée par des mécanismes très variés.

La contamination est d'autant plus facile que les éléments de la viande constituent le milieu nutritif par excellence, couramment employé en bactériologie.

Les chances de contamination sont d'autant plus grandes que la viande est soumise à des manipulations plus nombreuses; aussi, les aliments contaminés se recrutent—ils se trouvent généralement parmi les viandes dites travaillées: hachis, saucisses, cervelas, pâtés, et produits divers de charcuterie.

Les produits de charcuterie sont d'autant plus menacés que l'adjonction d'ingrédients variés permet d'y incorporer des viandes douteuses ou avancées, dans lesquelles les germes de toutes natures ont pu se multiplier à loisir.

La contamination est susceptible d'être provoqué par plusieurs causes.

(*a*) L'une quelconque des personnes appelées à manipuler les aliments peut être infectée. L'infection se traduit chez elle par une infection bénigne, telle que l'embarras gastrique, trop bénigne pour entraver les occupations habituelles; ou bien il s'agit d'une infection plus grave, soit avant, soit après l'évolution des symptômes sévères. Dans ces diverses circonstances comme nous l'ont démontré nombre d'épisodes épidémiologiques, le sujet infectieux peut contaminer tous les ailments, y compris les viandes. La contamination se fait probablement par l'intermédiaire des mains, si l'intéressé ne prend pas quelques précautions élémentaires de propreté.

(*b*) Au même titre, les ailments peuvent être contaminés par des porteurs de bacilles paratyphiques. La plupart de ces derniers ont été atteints antérieurement d'une affection paratyhoïde, parfois fruste

et méconnue. Ils peuvent demeurer contagieux pendant plusieurs années.

(*c*) Le contact d'une viande saine avec une viande infectée, ou bien avec des instruments ou des ustensiles malpropres, suffit à provoquer la contamination de quantités importantes d'aliments. Ce mode de contamination intervient tout spécialement dans le commerce de la charcuterie, où les mélanges sont fréquents et les manipulations nombreuses.

Quelques auteurs ont avancé qu'on trouvait assez souvent des bacilles paratyphiques dans des aliments parfaitement sains contaminés, sans danger pour l'homme. La chose est possible; il n'y a rien d'invraisemblable à ce qu'il existe dans les milieux extérieurs des Salmonelloses inoffensives pour l'homme. Toutefois, les expériences apportées à l'appui de cette conception ont été depuis plutôt infirmées que confirmées, et par suite on ne peut les considérer comme irréfutables. D'autre part, les échantillons de microbes rencontrés en pareil cas, tout en présentant les caractères cultureux et morphologiques des Salmonelloses, n'ont généralement pas été soumis au contrôle de l'action spécifique des sérums, qui constitue un critérium indispensable. La question reste à l'étude et mérite d'être suivie.

Pour le moment, nous ne pouvons pas considérer comme suspecte toute viande, travaillée ou non, infestée par des Salmonelloses bien caractérisées. L'expérience nous a trop nettement démontré que de tels aliments sont d'ordinaire toxiques pour l'homme.

(B) *Lait.*—Comme pour la viande, le lait peut être infecté soit par suite d'une maladie de l'animal, soit par suite d'une contamination accidentelle:

1°. En cas de mammite, provoquée par les Salmonelloses, chez la vache, le lait peut être profondément infecté.

2°. Un lait, pur à l'origine, peut être contaminé ultérieurement:

(*a*) Par l'un ou l'autre des mécanismes indiqués à propos de la viande;

(*b*) Par addition d'eau souillée.

Les bacilles paratyphiques peuvent passer dans les eaux avec les déjections, les urines, les eaux de lavage de boucheries, d'abbatoirs, etc.

IV. ÉTIOLOGIE DES INFECTIONS HUMAINES À SALMONELLOSES.

L'homme, très réceptif à l'égard de la plupart des Salmonelloses, peut être infecté de diverses manières.

1°. *Par contagion directe de malade à sujet sain.*—Cette contagion directe est beaucoup plus fréquente dans les infections paratyphoïdes que dans les empoisonnements alimentaires.

C'est remarquable de constater que la forme clinique des atteintes secondaires, par contact, est généralement identique à l'atteinte primi-

tive, contagionnante. Une infection paratyphoïde donne naissance au syndrome d'infection paratyphoïde, et non pas au syndrome d'empoisonnement alimentaire; il en est de même, mutatis mutandis, en cas de contagion secondaire des empoisonnements alimentaires.

2°. *Par contagion indirecte.*—Cette contagion se fait par l'intermédiaire des aliments infectés.

(*a*) L'infection peut venir de l'homme lui-même: contagion des aliments par le personnel appelé à les manipuler; contamination des eaux de boisson, des eaux de lavage, etc. Les formes cliniques observées en pareil cas sont très variables; tantôt infection paratyphoïde, tantôt empoisonnements alimentaires.

(*b*) L'aliment, provenant d'un animal malade, peut être infecté dès l'origine. De tels aliments engendrent régulièrment chez l'homme des empoisonnements alimentaires.

V. RAPPORTS DES DIVERSES SALMONELLOSES ENTRE ELLES.

1°. Au point du vue clinique, les affections provoquées par les Salmonelloses chez l'homme ou chez les animaux sont des plus disparates.

Entre ces diverses Salmonelloses, la bactériologie ne reconnaît cependant actuellement aucune différence appréciable; il en est ainsi particulièrement du bacille paratyphique B des infections paratyphoïdes humaines et du bacille type aertrycke des empoisonnements alimentaires.

Cette diversité de réaction clinique en présence de microbes en apparence identiques est un peu troublante.

Pour l'expliquer, Trautmann en fait appel à une conception ingénieuse bien connue. "L'intoxication par la viande est une forme aigüe, le paratyphus une forme sub-aigüe, d'une maladie infectieuse, une au point de vue étiologique." C'est-à-dire que l'ingestion de microbes en petite quantité, susceptibles des pullules peu à peu dans l'intestin, déterminerait un malade à évolution relativement lente; tandis que l'affection aiguë succéderait à l'ingestion d'une grande quantité des mêmes microbes avec leur toxine.

Cette conception me paraît en partie exacte; toutefois, elle n'explique pas tout.

Diverses raisons empruntées, partie à l'observation, partie à l'expérimentation, amènent à croire qu'en réalité certaines Salmonelloses tout douées originellement de propriétés toxiques, qui font défaut chez d'autres; et inversement, ces dernières peuvent être douées de propriétés infectieuses, marquées par leur tendance à la généralisation, qui sont exceptionnelles chez les premières.

Malgré leur identité apparente, j'estime que les bacilles carnés et les bacilles paratyphiques doivent être considérés comme pourvus de fonctions biologiques un peu différentes, les premiers surtout toxiques, les seconds surtout infectieux.

Ces différences biologiques sont d'ailleurs surtout accusées dans les types extrèmes, entre lesquels il existe certains intermédiaires.

2°. D'autre part, parmi les Salmonelloses il existe certainement des espèces peu virulentes pour l'homme. Il semble en être ainsi en particulier de la plupart des virus des rongeurs. Ces derniers, en effet, malgré le commerce considérable dont ils sont l'objet, ne paraissent avoir infecté l'homme que d'une manière exceptionnelle. La rareté même de ces infections suffit à montrer que tout au moins des nuances biologiques séparent ces virus des Salmonelloses habituellement pathogènes pour l'homme; l'existence indéniable des accidents qu'ils peuvent provoquer chez l'homme suffit d'autre part à démontrer que ces nuances biologiques ne sont pas irréductibles.

3°. L'expérience a montré que la viande des porcs atteints de pneumo-entérite n'est toxique pour l'homme que d'une manière exceptionnelle.

On peut accepter à l'heure actuelle que la toxicité existe exclusivement dans le cas où il s'est produit une infection secondaire par le bacille de Salmon. En toute autre circonstance, la viande peut être contaminée sans danger.

À cet égard, l'histoire du choléra du porc est identique à celle de la diarrhée, de la pyohémie, du veau, des abcès du cheval, etc.; ces diverses maladies infectieuses sont en effet susceptibles d'être provoquées par des microbes variés; la viande n'est dangereuse que si l'agent infectieux est pathogène pour l'homme.

4°. La comparaison des faits suggère l'opinion que les Salmonelloses se sont accoutumées peu à peu à telle ou telle espèce animale, à l'égard de laquelle elle se montre particulièrement offensive dans les conditions naturelles: bacille paratyphique B chez l'homme, bacilles carnés chez les bovidés, virus des rongeurs chez les rongers, etc. Mais ces fixations relatives n'ont rien d'absolu, et ces mêmes microbes sont aptes à infecter d'autres espèces animales, quand les circonstances s'y prêtent; et l'homme, en raison de son alimentation carnée, y est particulièrement exposé.

VI. PROPHYLAXIE.

1°. *À l'égard des individus contagieux.*—(*a*) Il est nécessaire de soumettre à l'isolement tout individu atteint d'une infection provoquée par les Salmonelloses.

Les malades présentant la forme clinique dite infection paratyphoïde ne doivent pas être mélangés avec les malades atteints de fièvre typhoïde.

Il serait désirable que l'isolement soit maintenu jusqu'à ce que les bacilles aient certainement disparu des excréta.

On prendra les mêmes mesures de désinfections qu'à l'égard de la fièvre typhoïde.

(*b*) Certaines professions méritent une attention spéciale, en raison de ce que leurs adhérents prennent part à la manipulation des aliments; spécialement le personnel des boucheries, charcuteries, des cuisines, des services des restaurants et hôtels, etc.

On a le droit de demander que dans les établissements ouverts au public, tout ce personnel soit soumis à une surveillance médicale constante, tant au moment de l'embauchage que pendant la durée de son service. Au premier signe d'infection, tout individu suspect serait éloigné et soumis à un examen médical et bactériologique, dont les résultats dicteraient la mesure à prendre. Une indemnité raisonnable serait attribué à l'intéressé.

2°. *À l'égard des animaux malades.*—La surveillance sanitaire de tout animal destiné à l'alimentation humaine est indispensable.

(A) Elle doit être pratiquée:

(*a*) Avant l'abattage, pour reconnaître les symptômes, diarrhée, état fébrile, de certaines maladies qui peuvent ne déterminer aucune lésion anatomique appréciable.

(*b*) Après l'abattage, en vue de déceler toute lésion pathologique.

Pour chaque animal suspect, il serait nécessaire de procéder à l'examen bactériologique (examen direct, culture) du tissu musculaire, du foie et de la rate. L'existence en quantité appréciable de bacilles appartenant certainement au groupe des Salmonelloses entraînerait la saisie totale (la stérilisation par la chaleur est insuffisante), avec indemnisation du propriétaire.

(B) L'application stricte de la surveillance sanitaire des animaux exige une inspection obligatoire et généralisée.

Elle doit être organisée dans les pays où elle n'existe pas encore.

Cette inspection ne peut être assurée que par des personnes compétentes, vétérinaire, ou à défaut, médecin. Il est illusoire et il pourrait être dangereux de confier un tel service à des personnes d'une compétence douteuse.

L'inspection.—Afin de permettre le fonctionnement du service d'inspection, les abattages ne doivent avoir lieu qu'exclusivement dans des abattoirs publics, soumis à une surveillance permanente. Comme conséquence, suppression complète des tueries particulières.

3°. *À l'égard des industries de travail ou de débit des viandes (charcuteries, etc.).*—(*a*) En ce que concerne l'état de santé des personnes, il serait nécessaire de les soumettre au régime prévu en 1° (*b*) ci-dessus.

(*b*) La propreté la plus méticuleuse sera constamment observée, tout en ce qui concerne les soins corporels des personnes que l'entretien des instruments, utensiles et locaux.

(*c*) On interdira avec la dernière rigueur l'emploi de viandes de mauvaise qualité.

(*d*) La création d'ateliers centraux de charcuterie, préconisée de divers cotés, pour faciliter la salubrité des opérations et la surveillance sanitaire est une œuvre logique et recommandable.

4°. *Précautions familiales.*—(*a*) Les personnes qui utilisent les virus des rongeurs seront prévenues du danger éventuel de ces virus pour l'homme et des mesures à prendre pour éviter tout accident.

(*b*) Dans tous les pays où les empoisonnements par les Salmonelloses sont quelque peu fréquents, il est indiqué de limiter au strict minimum la consommation de viande à l'état crû. Le public doit être reseigné à cet égard.

RÉSUMÉ.

I. Les Salmonelloses comprennent comme espèces principales les bacilles d'empoisonnements alimentaires (types Gärtner et type Aertrycke), le bacille paratyphique B, les virus des ronjeurs, quelques échantillons de bacilles du hog cholera.

L'action des sérums spécifiques sépare les Salmonelloses en deux sous-groupes.

Appartiennent exclusivement aux Salmonelloses les microbes qui présentent, outre les caractères généraux indispensables, la propriété d'être agglutinés ou de provoquer la déviation du complément en présence de l'un ou l'autre des sérums spécifiques pour chacun des deux sous-groupes.

II. Les Salmonelloses sont très répandues. On les rencontre entre autres: Chez l'homme malade, dans les infections paratyphoïdes et les empoisonnements alimentaires; chez les animaux de boucherie, au cours de maladies diverses; dans certaines épizooties des rongeurs; dans divers aliments contaminés; parfois chez l'homme ou les animaux à l'état sain.

III. Les aliments animaux le plus fréquemment infectés sont les viandes et le lait.

(A) *Viandes.*—L'infection peut provenir de ce que l'animal était atteint d'une maladie provoquée par une Salmonellose; ce sont les viandes dites malades. La maladie de l'animal peut s'accompagner ou non de lésions anatomiques appréciables. Dans tous les cas, c'est la septicémie qui coustitue le phénomène le plus important.

La présence éventuelle de Salmonelloses dans la viande d'animaux sains n'a rien d'impossible, mais ne paraît pas constituer un danger sanitaire sérieux.

Une viande primitivement saine peut être infectée après abatage (viandes contaminées). Les mécanismes de contamination sont très variés; il faut citer en première ligne le rôle des personnes appelées à manipuler les aliments dans les cuisines, les charcuteries, etc. La contamination peut se produire également par contact avec des aliments infectés, avec des instruments malpropres, etc.

Il n'est pas démontré que des Salmonelloses bien caractérisées puissent exister dans les aliments sans provoquer d'accidents.

(B) *Lait.*—Mêmes mécanismes de contamination que pour la viande. En plus, contamination par l'eau souillée.

IV. L'homme peut contracter des infections à Salmonelloses, soit par contact direct, soit par ingestion d'aliments ou d'eaux contaminées.

V. Les diverses Salmonelloses, identiques les unes aux autres devant la bactériologie, diffèrent probablement par certaines propriétés biologiques.

VI. La prophylaxie doit viser:

(*a*) L'individu contagieux: isolement désinfection.

(*b*) La surveillance sanitaire de tous les individus prenant part aux professions alimentaires.

(*c*) La surveillance des animaux de boucherie, avant et après l'abatage, avec inspection obligatoire et généralisée.

(*d*) La surveillance des ateliers de charcuterie.

(*e*) L'éducation du public en ce qui concerne l'emploi des virus des rongeurs et le danger possible des viandes crues.

REPRESENTATIVES OF THE GÄRTNER GROUP ISOLATED FROM THE TISSUES OF LABORATORY ANIMALS.

JOHN C. TORREY, Ph. D., Assistant Professor of Experimental Pathology and Lecturer in Hygiene, Cornell University Medical College, New York City.

It is generally agreed that our knowledge of the occurrence and distribution of the *B. enteritidis* of Gärtner in nature, aside from its presence in infected meat, is still far from complete. This bacillus has frequently been isolated from meat, and, to a less extent, also from vegetable foods which have been the causative factors in more or less severe outbreaks of food poisoning, but little light has generally been shed on the ultimate source of these bacilli nor on the mode of infection of the foodstuffs. It is my desire to invite your attention to a distributing vehicle for these bacilli which seems to be of considerable importance and which has hitherto been entirely overlooked.

In the course of an investigation into the etiology of canine distemper—an epizoötic centering generally in the respiratory tract and affecting primarily the mucous surfaces throughout the body—I have found that the *Bacillus enteritidis* (Gärtner) is frequently encountered in the organs of dogs suffering from this infectious disease. This bacillus is not the cause nor even an important factor in the disease, but occurs as a more or less sporadic invader of the tissues.

An important symptom of the severer type of canine distemper is a bloody mucous diarrhea associated with a more or less intense enteritis, and induced primarily by the toxin of the distemper bacillus (*B. bronchisepticus*). On autopsy, the mucosa may be found to be eroded and highly congested throughout the large and small intestine. It seems probable, accordingly, that the presence of these Gärtner bacilli in certain organs of the dog is due to their gaining access to the lymph or possibly the blood stream through this weakened intestinal epithelium.

In a series of 63 consecutive cases of natural and experimental canine distemper, which have been examined carefully bacteriologically, the *B. enteritidis* (Gärtner) has been found in one or more of the internal organs of 12 dogs, or 19 per cent. As will be presently demonstrated, these bacilli are identical with stock cultures of the *B. enteritidis* (Gärtner) of definite history and reliable source. These bacilli have been encountered most frequently in the liver, next in the spleen, and, more rarely, in the kidney, lungs, and blood. In some instances only a few colonies of this bacillus have appeared on the plates; whereas, in others, the organs seemed to be swarming with them. Such was the finding in a distemper dog which had succumbed to a lobular pneumonia. In the consolidated parts of the lung the Gärtner bacillus was recovered in pure and luxuriant culture, while in the unaffected lung areas, and in other organs, there were none present. One dog, which had suffered a relapse and was very weak, was found to be fairly swarming with the *B. enteritidis*, as it was recovered readily from the blood, the respiratory tract, the liver, spleen, and kidney, and in almost pure culture from the large and small intestine.

As a control for these distemper dogs a series of 19 normal dogs were examined. The *B. enteritidis* was found in the organs of only one of these and in small numbers in the spleen. Further, the agglutinins in the blood of this animal indicated that it had only recently recovered from an attack of distemper.

This bacillus apparently does not, as a rule, invade the viscera nor multiply in the intestinal tract until the final stages of the disease, when the vitality of the animal is seriously impaired by the distemper virus, for of the positive findings, 75 per cent occurred in animals which were undergoing a severe attack of the disease. In this series of 63 cases of distemper there were 28 dogs which were either dead at the time of culturing, or were beyond the prospect of recovery, and, from the organs of these severe or fatal cases, the *B. enteritidis* was recovered in 9 instances, or in 32 per cent, whereas, among 35 dogs which were suffering from mild attacks of distemper, or which were autopsied in the early stages of the disease, the Gärtner bacillus was recovered from only 3, or 8.5 per cent. It

would seem, then, that about one-third of the dogs which suffer severe attacks of distemper are harboring and probably eliminating the meat-poisoning bacillus of Gärtner.

In a series of 18 dogs in which material from different portions of the intestine was plated out on Endo medium the *B. enteritidis* was isolated in two individuals, or 11 per cent. One of these was an animal which had recently recovered from distemper, and the *B. enteritidis* was found in small numbers in the rectum. The other dog was dying from distemper and uncinaria infection. Endo plates, seeded with the content of both the small and large intestine, were crowded with colonies of *B. enteritidis;* in fact, this bacillus was present in almost pure culture. The blood, and such of the organs of this dog as were plated, were also impregnated with large numbers of the bacillus. It is evident that such a case might serve as a dangerous distributor of this bacillus.

This investigation has not been carried far enough to justify a definite statement in regard to the frequency of this bacillus in the intestinal tract of not only apparently normal dogs, but especially dogs dying with distemper, nor have the methods used thus far been the most favorable. I believe, however, that a considerable percentage of normal dogs harbor the *B. enteritidis* in the intestine, although in such very small numbers that their isolation is a matter of considerable difficulty, but during a severe attack of distemper these bacilli begin to multiply, and in the last stages may become the dominant microörganism in the intestinal flora, as was the case in the example just cited. This multiplication is no doubt greatly favored by the devitalizing action of the distemper virus, and especially by the fact that it may be accompanied by an intense inflammation and a very active secretion of mucus by the intestinal epithelium, which, as Pies has pointed out, facilitates the growth of bacilli of the typhoid group.

In the course of an investigation into the nature of a destructive cheesy pneumonia occurring among laboratory white rats a bacillus identical in every way with the *B. enteritidis* recovered from dogs was isolated from the lung of one individual.

As cats are susceptible to distemper, and also enjoy a natural immunity to the *B. enteritidis*, it was considered possible that they, like dogs, may harbor these bacilli. The results thus far with normal cats have been negative. Endo plates made from the liver and spleen have always proved sterile, and from the intestinal content no bacilli have been isolated which are identical with the meat-poisoning bacillus, although types which induce a typical alkalinity in litmus milk and ferment glucose with gas production, but not lactose, are common, as they are also in the intestinal flora of the dog. None of

them, however, ferment dulcit, and they failed to agglutinate with any paratyphoid serums in dilutions higher than 1–200. They conform to one or more of the types of Morgan's bacillus. The *B. proteus vulgaris* is also common in the intestinal flora of both animals.

These bacilli isolated from dogs are identical culturally with stock cultures of the *B. enteritidis* (Gärtner). They are motile, Gram-negative bacilli of typical morphology. They do not produce indol in peptone water, but reduce nitrates to nitrites and ferment with gas production the carbohydrates, dextrose, levulose, galactose, maltose, mannit, dulcit, and sorbit, but not lactose, saccharose, adonit, raffinose and inulin. They produce 30 to 50 per cent of gas in dextrose broth, and the Voges-Proskauer reaction is negative. With litmus milk, the initial acidity gives way in two or three days to an increasing alkalinity, which in two to three weeks becomes intense.

That these cultures isolated from dogs, and also the culture from the white rat, are the *B. enteritidis* of Gärtner, and not some other species of the enteritidis group, is conclusively proved by agglutination experiments. The two stock cultures with which they were compared were obligingly furnished by the department of public health of the American Museum of Natural History, New York—one of them came originally from the Rockefeller Institute and the other from Kràl. The culture of *B. cholerœ suis* was received from the same source and was originally isolated by Dr. Billings from hog cholera. The representative of the paratyphoid B group is a Schottmüller strain. The antisera were prepared by inoculating rabbits intraperitoneally.

CHART I.

Identification of B. enteritidis cultures from dogs and rat by agglutination experiments.

Cultures.	Antiserums.			
	B. enteritidis, No. 132 (Gärtner).	Dog bacillus No. 59.	B. cholerœ suis.	B. paratyphosus, B.
1. B. enteritidis, No. 18 (Gärtner)	32,000	32,000	50	50
2. B. enteritidis, No. 132 (Gärtner)	32,000	32,000	50	50
3. Dog bacillus, No. 69, liver	24,000	32,000	<50	<50
4. Dog bacillus, No. 82, intestine	24,000	32,000	<50	<50
5. Rat bacillus, lung	24,000	32,000	<50	<50
6. B. cholerœ suis	<200	<100	20,000	<50
7. B. paratyphosus, B. (Schottmüller)	<200	<100	50	2,000

As is shown in the chart the stock cultures of *B. enteritidis* and the dog and rat cultures interagglutinate, whereas none are clumped except in very low dilutions by antisera to the *B. cholerae suis* and

B. paratyphosus, *B.* Nor do these two cultures interagglutinate with the anti-*B. enteritidis* serum or with the anti-dog-culture serum. With a single exception all the cultures isolated from dogs, culturally like *B. enteritidis*, agglutinated with striking uniformity and practically to the limit of the serums immune either to the dog cultures or to the stock *B. enteritidis* cultures, and all evidently belong to the same strain. In the one exception, the culture isolated from the liver of a certain dog agglutinated well, whereas cultures from the spleen, although absolutely identical culturally with the *B. enteritidis*, failed both to agglutinate with enteritidis serum and also to absorb any specific agglutinin for the same. Stromberg has described similar nonagglutinating strains of the *B. enteritidis* and considers them degenerated forms.

Absorption experiments provide the last link in the proof that these cultures isolated from distemper dogs are true representatives of the *B. enteritidis*. No attempt was made to exhaust the serums in these experiments, but the results show conclusively that the dog cultures can absorb the specific agglutinins from an enteritidis (Gärtner) serum and also that the stock *B. enteritidis* cultures absorb the specific agglutinins from a serum immune to a dog culture. Absorptions seem to offer a rational and conclusive mode of identifying these bacilli of the paratyphoid group, but in many investigations have been neglected.

Strangely enough no specific agglutinins for these bacilli were produced in the blood of the dogs which harbored them, although in one instance they were found in great abundance throughout the body.

These cultures from dogs are highly virulent for rabbits, guinea pigs, and white mice (as has been reported to be the case with strains of the *B. enteritidis* from other sources), decidedly less toxic for white rats and cats, and not at all so for dogs. For guinea pigs they revealed a toxicity fully 10 times as great as the stock cultures of *B. enteritidis* (Gärtner), 0.001 of a cubic centimeter of a 24-hour broth culture proving fatal in 24 hours. Rabbits were killed by 0.1 cubic centimeter in 24 hours and by 0.01 cubic centimeter in 5 days, when inoculated intraperitoneally. One-tenth of an agar culture, sterilized by heat, also proved fatal, indicating that the toxin is to a certain extent heat resistant, as is known to be the case with Gärtner's bacillus. White mice are exceedingly susceptible, as 0.001 cubic centimeter of a 24-hour broth culture, inoculated intraperitoneally, killed in 24 hours, and 0.0001 in 3 days; on the other hand, white rats seem to enjoy a relative immunity, as about 0.5 cubic centimeter intraperitoneally was required to kill. Two cubic centimeters inoculated intraperitoneally into a cat caused a diarrhea and sickness, fatal within 14 days.

In the study of the virulence of bacilli of the enteritidis group, feeding experiments are of value and interest. With these dog cultures I was not successful in inoculating white rats by feeding, but with white mice the results were striking and uniformly successful. The culture used was a strain isolated from the intestine of a distemper dog. Mice fed on bread moistened with an emulsion of this bacillus sickened in three to five days and died in four to six days. Autopsy showed a congested condition of the small intestine and a bloody mucous content, the spleen was much swollen and dark, and the liver embodied more or less extensive and scattered necrotic areas; there appeared also in certain instances a congested state of the lungs with some consolidation. Pure cultures of these bacilli were recovered from the heart blood, the liver, and the spleen.

As is well known, the *B. enteritidis* (Gärtner) is not toxic for the dog, and the enteritidis cultures isolated from the dogs themselves proved no exception to this rule. A puppy withstood the intraperitoneal inoculation of several thousand times the fatal dose for rabbits without ill effect. The subcutaneous inoculation of large doses of this bacillus produced a more or less extensive gaseous swelling, but the animal seemed to suffer little, if any, discomfort. This tolerance of the dog to the meat-poisoning bacillus seems of considerable importance, as it permits a great increase of the bacilli within the body and a long period of elimination before death from distemper ensues.

As far as I am aware, there is no record in the literature of the *B. enteritidis* (Gärtner) being isolated from dogs. Although members of the intermediate group have been reported as occurring in these animals, yet the identification has not been definite. Ruediger, in the Philippines, has reported the isolation of a paratyphoidlike bacillus from the blood and organs of a dog examined for Negri bodies. This bacillus was culturally like the intermediate group, but its specific affinities could not be determined by agglutination—no enteritidis serum was available. Courmont and Rochaix, also Vallet and Reinbaud, have described intermediates as occurring with more or less frequency in the fecal discharges of dogs, especially those of the street. These bacilli were not specifically identified, however, and, from the descriptions, many were atypical *B. coli*. Aside from these reports, the importance of the dog as a distributor of bacilli of the paracolon group has never been realized. Bacilli of this group have occasionally been reported as associated with epizoötics among guinea pigs and rabbits in various parts of the world. O'Brien and Petrie recovered the *B. suipestifer* from victims of one outbreak, and Bainbridge and O'Brien the *B. enteritidis* from another. Boycott has described an infective methemoglobinuria oc-

curring naturally among white rats, caused by the *B. enteritidis*, and prevailing to the extent of 1 per cent of the total number. Rat viruses are commonly prepared with strains of the *B. enteritidis* and this bacillus may be more or less widely distributed through these animals. This bacillus, or nearly related ones, have been described as the cause of enteritis in a considerable variety of birds and mammals other than those already specified.

Granting that these strains of the *B. enteritidis*, which occur under varying conditions in animals, may possess infective properties for man—and, although there is not sufficent evidence for generalization, in certain instances they have been proved to possess such a character—the dog apparently presents the greatest source of danger as a distributor of the meat-poisoning bacillus of any of the domestic animals, coming, as it does, in close and generally almost unrestricted contact with man and his food products. It is noteworthy that distemper is exceedingly common among young dogs, and that a very high percentage of street dogs suffer from the infection during the first years of life, with a death rate of 30 per cent, or higher. Dogs are very commonly kept by farmers and dairymen, and generally have free access to the stockyards and stalls of the cattle. A certain proportion of them inevitably suffer from an attack of distemper, and it is quite possible that they are at times in a position to infect live stock with the Gärtner bacillus, either directly, or indirectly through their food, and also the milk.

It may also be the case that certain of the obscure cases of food poisoning, especially those which have been induced through the consumption of infected vegetable foods, may have their ultimate explanation in the contact of distemper dogs with such commodities.

The obvious conclusion from these findings is that it is safer to exclude carefully dogs suffering with distemper from all possible contact with food and live stock, and it should be borne in mind that the danger from these animals as the eliminators of the *B. enteritidis* increases as death approaches.

BACTERIOLOGICAL EXAMINATION OF MARKET MILK.

Dr. P. G. Heinemann, Department of Bacteriology, University of Chicago, Ill.

This investigation was carried on with the object of determining whether a reliable indicator of methods of producing milk could be found. The samples were bought in the open market in original packages; 215 samples were examined. Of this number, 108 samples were raw milk, and 107 samples pasteurized milk. The samples were

carried to the laboratory packed in ice and examined immediately after arrival. The following determinations were made:

1. The amount of dirt was ascertained by the method described by Torrey.[1] The results were expressed in milligrams per liter.

2. Counts of colonies per cubic centimeter of milk were made and the acid colonies counted separately.

3. The number of bacteria of the *B. coli* group in 10 cubic centimeters of milk was determined by inoculating 1 cubic centimeter and 0.1 cubic centimeter of milk each in five fermentation tubes containing 1 per cent dextrose infusion broth.

4. The number of aerobic spores was determined by inoculation of 1 and 0.1 cubic centimeters milk each in five tubes of litmus milk, and the tubes heated to 85° C. for 15 minutes.

5. The number of anaerobic spores was determined by inoculation of 1 and 0.1 cubic centimeters of milk each in five tubes of litmus milk. The tubes of litmus milk were heated to the boiling point previous to inoculation and after inoculation heated to 85° C. for 15 minutes. The surface of the milk was then covered with a layer of mineral oil, previously sterilized by boiling.

A summary of the results of this investigation leads to the assumption of the following facts:

1. The average number of colonies per cubic centimeter in 108 samples of raw milk was 4,804,300, in 107 samples pasteurized milk. 1,772,100.

2. The percentage of acid colonies in raw milk was 31, and in pasteurized milk, 28.

3. The average number of bacteria of the *B. coli* group in 10 cubic centimeters raw milk was 14; in 10 cubic centimeters pasteurized milk, 19.

4. The average number of aerobic spores in 10 cubic centimeters raw milk was 47; in 10 cubic centimeters pasteurized milk, 63.

5. The average number of anaerobic spores in 10 cubic centimeters raw milk was 46; in 10 cubic centimeters pasteurized milk, 61.

6. The average number if milligrams dirt per liter of raw milk was 2.2; of pasteurized milk, 1.4.

I conclude from these results that:

1. Commercially pasteurized milk turns sour the same as raw milk, and that there is no consistent relation between acid colonies and the total number of colonies.

2. Pasteurized milk contained less dirt than raw milk. The proportion was as 11 for raw milk to 7 of pasteurized milk. The method employed shows, however, the insoluble dirt only.

3. The relation of the number of bacteria of the *B. coli* group in raw milk to the number in pasteurized milk was as 9.5 to 7. This shows that either some of the milk sold as pasteurized was not effi-

ciently pasteurized, or that there are some highly resistent forms of *B. coli* which survive pasteurization.

4. The relation of the number of aerobic spores in raw milk to the number in pasteurized milk was as 3 to 4.

5. The relation of the number of anaerobic spores in raw milk to the number in pasteurized milk was as 3 to 4.

6. There was no relation between the number of bacteria of the *B. coli* group, or of the aerobic spores and anaerobic spores to the total number of bacteria or to the acid colonies.

7. The temperature of milk during transportation is a variable factor, and the relation of groups of bacteria in milk is probably shifted by multiplication. The results obtained in this investigation can therefore have no bearing on the relation of groups of bacteria in freshly drawn milk.

8. Total counts seem to be the only means of judging methods of production and transportation. By this method we can not distinguish definitely between methods of production and transportation. However, a large proportion of acid colonies, accompanied by a small amount of dirt, would indicate faulty transportation, and a small proportion of acid colonies and a large amount of dirt would indicate faulty production. When both production and transportation are faulty, one may expect to find large total numbers, a large number of acid colonies, and a large amount of dirt. By making these three tests a fairly accurate insight into the quality of the milk may be obtained.

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[1] Amer. Jour. of Public Health, 1912, vol. 2, p. 280.

DISCUSSION.

Dr. W. H. PARK: There are only two points upon which I can not quite agree with the paper of Dr. Henderson Smith, and I wish to comment upon these. He has concluded that the dysentery types other than Shiga are not constant, and that the absorption agglutination test is not of great value in differentiating the different stains. In the United States the workers have found that the maltose-fermenting type and the manite-fermenting type are equally stable and distinct, and with the more important Shiga type are the exciting factor in the great majority of cases of dysentery. The small percentage of cases remaining seems to be due to quite a number of other varieties. In Germany also, I believe, it is recognized that these groups exist. The cultures obtained by Hiss, myself, and others have in cultural and agglutination test fallen into these groups and continued true in their characteristics. In a broad sense this is probably true throughout the world, although in special localities bacilli of different characteristics may predominate. I believe in patho-

genic varieties of bacteria the agglutination characteristics are as important as fermentation characteristics.

Dr. W. Fornet, Berlin, gibt Herrn Smith darin Recht, dass ein grosser Teil der bei der Differenzierung von Paratyphus- und paratyphusähnlichen Bazillen entstandenen Schwierigkeiten dadurch vermieden worden wäre, wenn alle Untersucher nur sichere Paratyphusbazillen als Vergleichsobjekte benutzt hätten. Dies ist nicht der Fall. Beschränkt man sich darauf, zunächst nur solche Bazillen mit entsprechenden kulturellen und biologischen Eigenschaften als Paratyphusbazillen zu bezeichnen, die aus dem Blut von paratyphuskranken Menschen gezüchtet waren. Unter Beobachtung dieser Vorsichtsmassregel ist es mir immer gelungen, mittels der Absortionsmethode nach Castellani den Paratyphus B. Bazillus von allen ähnlichen mit Sicherheit zu unterscheiden.

Herr Kollege Smith vom Lister Institut hat den Vorschlag gemacht, eine Kommission zu ernennen, die eine einheitliche Untersuchungsmethode für die Typhus-Coligruppe ausarbeiten soll. Dieser Vorschlag ist unterstützt worden von Herrn Präsident Welch und H. Stabsarzt Fornet und ich selbst habe in meinem Referat auf die Notwendigkeit, sich erst über eine einheitliche Untersuchungsmethode zu einigen, hingewiesen. Es ist dies der erste Schritt den wir thun müssen, um Klarheit in die verworrene Frage zu bringen. Ich möchte mir nun erlauben, gleich einige Vorschläge für die Zusammensetzung dieser Kommission zu machen, die natürlich ganz unmassgeblich sein sollen.

Iche möchte vorschlagen in erster Linie unsern verehrten Vorsitzenden Herrn Prof. Theobald Smith, Herrn Direktor Park und Herrn Kollegen Winslow, ferner das Lister Institut in London, H. Kollegen Smith, das Institut Pasteur in Paris, das Hygienische Institut der Universität Wien, Prof. Babes aus Bukarest, das Hygienische Institut der Universität Greifswald (Loeffler), das Institut für Infektionskrankheiten Robert Koch (Berlin) und das Kaiserliche Gesundheitsamt Berlin.

Es ist nun aber immer so eine Sache mit solchen über die Erde zerstreuten Kommissionen, ihre Tätigkeit und Wirksamkeit ist erschwert, ja in Frage gestellt, wenn nicht eine Centrale vorhanden ist, welche die Initiative übernimmt und die Verbindung mit den verschiedenen Mitgliedern aufrecht erhält. Sie hätte im vorliegenden Fall vielleicht auch den ersten Entwurf zu einem Plan für eine einseitliche Untersuchungsmethode der Typhus-Coligruppe aufzustellen und den andern Mitgliedern zur Äusserung zuzusenden. Vielleicht würden die amerikanischen Kollegen diese Centrale bilden.

Dr. E. Libman, Mount Sinai Hospital, New York: In much of the work done in recent years, an important fact has been lost sight of—that it is essential to use optimum media for determination and

production, a point emphasized many years ago by Durham. Most of the media now used are not sufficiently favorable, especially when one is dealing with organisms that grow well. In an extensive research made by Drs. Celler and Sophian and myself, in the laboratories of the Mount Sinai Hospital, it was found that agar plus carbohydrates was a most unfavorable medium for detection of acid production. And still that medium is most used. The next best medium is bouillon plus the carbohydrates. Still more favorable are agar media with serum and carbohydrates (we used ascitic serum). But the best media are made up from bouillon by the addition of serum and the various carbohydrates. I believe that a still better medium can be made up.

For a number of years the serum-water media have been much employed, both here and abroad. Hanna, in 1908, introduced a medium consisting of water 9 parts and ox serum 1 part, with carbohydrates and litmus. Hiss, a few years later, advised the use of a similar medium, but containing 2 parts of water and 1 of serum.

In 1905 Dr. Buerger advised the addition of 1 per cent of peptone to the last-mentioned serum-water medium. This medium is far superior to that made up without peptone, but is not quite as good as the media made up of bouillon serum and carbohydrates.

When our complete studies are published it will also be made clear that titre is important. Growth may be very poor in a medium without serum at a certain titre, and much better with serum at another titre. If optimum media will be more used by investigators than they are at present, it is very probable that we shall find less variants than are now believed to exist.

C. E. A. Winslow, New York: I have listened with great pleasure to these papers and particularly to the admirable treatment of the subject of variability by Dr. Smith. The investigations of the last few years, in which the workers at the Lister Institute have played a leading part, have made it clear that bacteria do vary, particularly when exposed to certain definite environments. If these variations are considered from a broad biological viewpoint, however, they offer no serious obstacle to scientific classification.

In the first place, the variations which occur, so far as carbohydrate fermentation is concerned, are of a definite and orderly character. We have worked this out in the case of the streptococci and have found that the sugars stand in a pretty regular order of availability. The monosaccharide, dextrose, is most easily attached. Then come the disaccharides, lactose, and saccharose and the glucoside, salicin. Raffinose is more difficultly utilizable and inulin and mannite still more so. There are exceptions to every rule in biology, but in general we find that streptococci which attack inulin and mannite can attack all the simpler carbohydrates, those which ferment raffinose

ferment the disaccharides, and those which ferment the disaccharides all utilize dextrose. The term "metabolic gradient" has been applied to this relationship and the differences between relationship and the differences between streptococci, according to this conception, are not haphazard, but consist in the addition or subtraction of a series of enzymes, each of which, superposed on the rest, makes available a new and more couple- carbohydrate.

In the colon group, it is interesting to note that the metabolic gradient is quite a different one. It is the size of the molecule which mainly controls assimilation with the streptococci. Those that attack lactose almost always attack saccharose equally well. The colon group, on the other hand, all break up lactose but only half of them ferment saccharose, and those that do can break up raffinose equally well. Here it is the configuration of the molecule not its size which determines availability. Aldehydic sugars are assimilated by all, while only one subgroup can ferment ketonic sugars. To those that have the latter power, the size of the molecule appears to be indifferent.

The practical difficulty we have to meet in classification is that offered by minutely integrading forms. Certain workers in England and in this country have come to the conclusion that there is just one way out of the dilemma of big heterogeneous groups on the one hand and innumerable varietal names or numbers on the other. That is the use of the statistical or biometric method. If you measure quantitatively the important characters of a considerable series of bacteria belonging to a group and plot them, you find that they group themselves naturally about certain modal points or centers of variation. To these type centers, about which the individual strains are varying, we can conveniently give specific names, regarding the rarer forms between as simply variants from the central types. By such a study of populations, rather than individuals, the relations of the puzzling group of the cocci have, I think, been made clearer than they were before, and more recently Dr. Howe and Dr. Morse, both of Boston, have applied the same methods to the colon group and the diphtheria group, respectively, with marked success. I may say, in passing, that so far as the colon group is concerned, Dr. Howe has in the main brought us back to the simple division into saccharose fermenters and nonsaccharose fermenters, which was pointed out by our chairman, Dr. Theobald Smith, so many years ago.

It does not in the least detract from the value of a statistical classification to say that under changing conditions the properties of the bacteria may change as well. As the populations of bacteria exist in nature, they do group themselves about definite type centers, which are perhaps habitat species molded to some extent by the conditions surrounding them, but real entities nevertheless, and the

only practical units which we have for the identification and classification of bacterial forms.

Dr. WILLIAM H. WELCH, Baltimore, Md.: In view of the confusion relating to the classification and differentiation of the so-called paratyphoid or intermediate group and of the great inequalities in the methods of studying this group I would suggest the desirability of appointing, with the approval of this congress, an international commission to consider the methods of investigation of bacteria of the Colon-typhoid group with a view of reaching an agreement at least as to the more essential tests which should be employed in the study and description of members of the group. Such a commission could perhaps report to the next congress, but it would be desirable to publish their conclusions as soon as formulated. This proposal is one which may perhaps be considered at the end of this meeting.

LA TUBERCULOSIS EXPERIMENTAL EN LAS GRANDES ALTURAS.

NESTOR MORALES, delegado de Bolivia ante el XV. Congreso Internacional de Higiene y Demografía en Wáshington.

He creído que seria de importancia para vosotros el conocer un aspecto aun no estudiado de la tuberculosis, cual es el que se refiere á la tuberculosis experimental en las grandes alturas.

El hecho es tanto más importante, cuanto que mientras en Europa ya á los 4,000 metros sobre el nivel del mar, existen las nieves eternas y la vida humana es casi imposible; en mi país existen á alturas que varían de 3,000 á 4,000 metros poblaciones florecientes, que tienen de 20,000 hasta 100,000 habitantes.

HISTORIA.

Sabemos cuales son las condiciones que facilitan la propagación y desarrollo del bacilo de Koch; entre estas tenemos en primer término el aire confinado, la miseria y un elevado grado higrométrico; es por esta razón que en las grandes capitales del Viejo Mundo, es donde la tuberculosis hace particular destrozo, mientras que las pequeñas poblaciones rurales y los habitantes del campo, son mucho menos atacados.

Sentado el principio que antecede, es fácil comprender que en las poblaciones bolivianas, donde la miseria es casi desconocida y en las cuales la aglomeración urbana es insignificante, y cuyo aire es constantemente calentado por un sol que no cesa de brillar en todo el año, la tuberculosis haya sido rara y quizá no haya existido, sino en época muy posterior.

Consultando las páginas de la historia médica de mi país, y muy especialmente del Departamento de La Paz, he obtenido la firme con-

vicción de que hasta el año 1880 la bacilosis era desconocida. Poco tiempo después, el movimiento comercial y las inmensas riquezas minerales del suelo boliviano, atrajeron una corriente de inmigración cuyos primeros representantes fueron los trabajadores peruanos y chilenos de la costa del Pacífico, y junto con ellos vinieron á medicinarse los primeros tuberculosos, atraidos por la belleza del clima y la acción saludable de la altura.

La Paz, población que cuenta en el momento actual con 100,000 habitantes, poco más ó menos, está situada á los 16° 29′ 30″ de latitud y á los 70° 19′ 40″ de longitud, siendo su altura de 3,665 metros. Su clima es benigno, siendo las temperaturas medias en verano y en invierno mui soportables; de manera que los calores sofocantes así como los excesivos fríos, son absolutamente desconcidos.

Se comprende pues, que las favorables condiciones del clima fueran debidamente apreciadas por los enfermos, muchos de los cuales curaron en condiciones sumamente satisfactorias, y los cuales al volver á su patria, ponderaron las inmejorables condiciones del clima de La Paz, lo que lógicamente atrajo una cantidad considerable de enfermos.

Á partir de los años 1886 y 1887, se empezaron á observar los primeros casos de tuberculosis indígena, y lo que es digno de llamar la atención, con un carácter de extraordinaria gravedad, como si el bacilo de Koch hubiese, al encontrar un terreno esencialmente nuevo, exaltado su virulencia, hasta el punto de que las bacilosis aquí observadas han tenido siempre una marcha subaguda y rápidamente mortal.

Otro hecho sobre el que me permito llamar la atencón de este ilustre Congreso, es que la tuberculosis ha manifestado particular predilección por la raza indígena, en la que se ha presentado con mucha mayor frecuencia que en la blanca ó mestiza.

La extraña marcha de la enfermedad, así como la circunstancia de que todos ó la mayor parte de los que venían de la costa se curaban en breve plazo, hacía importante el estudio bacteriológico experimental del bacilo de Koch, para darse cuenta exacta de las particularidades que ofrecía á la observación. Es respondiendo á esta necesidad, que el año próximo pasado empezé un estudio minucioso sobre la tuberculosis experimental en las grandes alturas.

INOCULACIONES CON CULTURAS EXTRANGERAS.

Con el propósito de dar la mayor amplitud posible á las investigaciones, me dirijí, de una manera oficial á los siguientes institutos, para que se sirvieran procurarme culturas puras de bacilo tuberculoso:

Instituto de Bacteriología del Departamento de Agricultura de Norte América, Instituto Pasteur de París, Instituto Real de Viena, Instituto de Higiene de Santiago de Chile, Instituto de Higiene de la República Argentina.

Las culturas se recibieron sucesivamente y este fué el resultado de las primeras investigaciones:

Culturas norteamericanas.—Se recibieron en fecha 10 de enero del año en curso, é inmediatamente se procedió á hacer una inoculación subcutánea en un cobayo de 360 gramos.

Observadas las temperaturas en la mañana y en la tarde, no se notó modificación apreciable, á excepción de un ligero aumento durante la tarde del primer día.

La reacción local se redujo á una pequeña induración en el punto inoculado, y al infarto ganglionar de los ganglios inguinales, infarto que en la segunda semana desapareció por completo, habiendo desde entonces el cobayo recobrado la salud. El peso disminuyó 10 gramos durante la primera quincena; pero luego volvió á elevarse hasta llegar á 400 gramos, sin que el animal volviera á presentar sintoma de ninguna especie. Seis meses despés, el animal continuo conservando un apetito excelente y una salud buena.

Cobayo No. 2.—Cultura de bacilo tuberculoso procedente de Viena, infectada de hongos. Viendo el resultado negativo de las primeras experiencias, pensé que probablemente la pequeña cantidad de bacilos inyectados en el primer caso habría sido insuficiente para determinar el proceso patológico de experimentación, y es por esta razón que, en esta segunda experiencia, se tomó una considerable cantidad de la cultura habiéndose inyectado en el peritoneo 2 centímetros cúbicos de una emulsión concentrada de bacilo de Koch. Las experiencias empezaron el 14 de marzo, con un cobayo cuyo peso era de 415 gramos en el momento de la operación. Dos meses después, como el animal no diera muestra de sufrir en lo más mínimo, sino que el peso se había elevado á 475, se resolvió sacrificar al animal, para ver si existían ó no en su organismo focos profundos de bacilosis de marcha crónica.

Verificada la autopsia, no se econtró un solo bacilo, y las culturas que se hicieron en suero glicerinado quedaron estériles.

Cobayo No. 3.—Cultura procedente del Instituto Pasteur de París. Cobayo de 420 gramos, inoculado en fecha 28 de febrero con 2 centímetros cúbicos de emulsión concentrada. En la tarde, elevación de temperatura á 39°, siendo la temperatura normal de los cobayos en esta altura 38° 6′. El animal está abatido, ha tomado poco alimento, lo que prueba que hay una acción toxi-infecciosa enérgica sobre su organismo. Al día siguiente, la temperatura ha vuelto al tipo normal, el apetito reaparece sin que el animal dé prueba de sufrir nada. Ocho días después, examinando los ganglios se puede notar un ligero infarto, el que va desapareciendo rápidamente, de manera que seis meses después el animal tiene 40 gramos de aumento en su peso y un estado de sanidad completa.

Cobayo No. 4.—Cultura del Instituto de Higiene de Chile. Cobayo de 435 gramos de peso, inoculación subcutánea, el 19 de abril, con

2 centímetros cúbicos de emulsión concentrada. La reacción es nula. Pasados veinte días, se presenta un punto indurado en lugar de la inoculación, el que se reblandece y da lugar á la producción de un pequeño absceso, en cuyo pus se pueden distinguir muy pocos bacilos. Sembrado el pus, tanto en suero glicerinado cuanto en geleosa glicerinada, no determina la producción de cultura. El animal pierde 15 gramos de su peso; pero á los ocho días, cicatrizada la pequeña ulceración, el peso aumenta llegando á 478 gramos.

Cuatro meses después, se comprueba un estado completo de sanidad en el cobayo.

En el caso anterior es indudable que se trataba de un proceso local de bacilosis, que no ha llegado á generalizarse, debido á la reacción defensiva del órganismo.

Cobayo No. 5.—Cultura procedente de la República Argentina. Peso de 460 gramos. Inoculado en fecha 20 de febrero con 2 centímetros cúbicos de emulsión concentrada. Resultado negativo. No habiéndose presentado reacción apreciable en ninguna forma.

Por la relación que antecede, se vé que las culturas de diferente procedencia, inoculadas sea en forma subcutánea ó intra-peritoneal han dado un resultado constantemente negativo. Habiéndose limitado las manifestaciones de defensa orgánica á fenómenos de poquísima importancia, los mismos que desaparecieron en corto plazo.

La interpretación de este fenómeno puede ser múltiple, y para la claridad de la exposición le dividiremos en tres grupos:

1°. Las culturas, á causa de un largo viaje, habían envejecido? Es decir, perdido sus primitivas propiedades, para convertirse en elementos inertes.

2°. El aumento de globulización en las grandes alturas, hecho comprobado por los estudios de Vergara Lope y de Viault, habían determinado una mayor potencia de reacción orgánica, y por consiguiente los elementos defensivos siendo en mayor número habían provocado una destrucción del elemento microbiano?

3°. Las culturas al llegar á un clima distinto del que habían vivido habían, en contacto de un medio nosológico estraño, habian perdido sus primitivas propiedades?

Estas serían las tres maneras de explicar el fenómeno observado con la inoculación de las culturas extrangeras.

La primera explicación no me parece plausible; pués, las resiembras dieron nacimiento á nuevas colonias, aunque en número menor y, por otra parte, es sabido que el bacilo tuberculoso, aun en contacto del aire y de la luz, elementos que le son absolutamente contrarios, guarda su virulencia durante un tiempo mucho mayor que el que tardaron las culturas en llegar á la ciudad de La Paz, algunas de las cuales, como las procedentes de la Argentina y Chile, sólo demoraron de 15 á 20 días.

La segunda explicación, que consiste en la mayor defensa orgánica fagocitaria, dependiente de la hiperglobulización, tampoco me parece satisfactoria, tanto más, cuanto que el papel defensive de los fagocitos ha perdido una parte de su valor, con los nuevos estudios del Profesor Ehrlich.

Nos queda, para explicar el fenómeno estudiado, la acción del medio nosológico, la que á mi juicio tiene mayores probabilidades de evidencia.

Efectivamente, sea que consideremos á las bacterias como á algas microscópicas anaclorofilianas, sea que en ellas veamos organismos de la escala zoológica inferior, el hecho es que, vegetales ó colocados en la serie animal, es indudable que sufren como todo ser organizado, la acción del medio ambiente, que en ciertas ocasiones les esteriliza por completo quitándoles su potencia reproductora.

No necesito mencionar muchos ejemplos ante esta ilustre asamblea, me bastará citar la falta de reproducción de los animales africanos en el medio europeo, y la falta completa de desarrollo de los vegetales de la zona tropical americana, en los climas fríos del norte ó del sur del continente.

Pero aun debo dar á conocer otras experiencias, que á mi jucio son absolutamente convincentes, una vez que demuestran con certidumbre completa la afirmación que acabo de sentar.

He dicho que la tuberculosis importada se cura en este clima de altura; he dicho también que la tuberculosis indígena tiene una marcha esencialmente grave. Traduciendo con otras palabras, podemos decir que el bacilo no aclimatado muere y que el bacilo que ha tomado carta de ciudadanía es eminentemente temible por su excepcional virulencia.

Las experiencias siguientes nos parecen particularmente interesantes:

Cobayo No. 1B (peso, 600 gramos).—Inoculado el 11 de julio de 1911 con esputo tuberculoso, procedente de un individuo de la costa de Chile, presentando gran cantidad be bacilos al examen microscópico. Falta completa de temperatura; quince días después ligera tumefacción en el punto inoculado, á los seis días se forma un pequeño absceso que se abre fuera, dando salida á un pus espeso, en el que se descubren bacilos de Koch. El peso no ha disminuído, el animal conserva un apetito satisfactorio; el 5 de agosto la herida ha cicatrizado por completo, el animal aumenta de peso. Conclusión: tuberculosis localizada, que termina por la curación.

Cobayo No. 2B.—Inoculado el 10 de octubre de 1911, con esputo tuberculoso comprobado por el examen microscópico. Peso, 540 gramos en el momento de la operación. El esputo provenía de una persona de la costa de Chile, que había venido á medicinarse á la ciudad de La Paz.

Los días siguientes, el animal sólo demuestra un ligero aumento de 5 centígrados en su temperatura ordinaria, hipertermía que desaparece al octavo día. No hay reacción local. Tres meses después el animal ha aumentado 15 gramos de peso. El apetito y la salud general se conservan en condiciones satisfactorias.

Cobayo No. 3B.—Inoculado en 12 de octubre de 1911. Inoculación intraperitoneal, esputo comprobado tuberculoso por examen microscópico, enfermo procedente de Chile. El 22 del mismo mes, elevación de temperatura á 39°; el cobayo está abatido y triste, los pelos levantados, el apetito nulo. Este estado se conserva durante ocho días, al cabo de los cuales el animal vuelve á recobrar el apetito, el peso que había disminuído en 50 gramos, empieza á elevarse nuevamente. Cuatro meses después el animal se encuentra completamente restablecido.

Llamo la atención sobre el hecho de que en esta serie de experiencias, que no quiero continuar detallándolas, pues siempre en todas las inoculaciones se obtuvo idéntico resultado, el esputo que se empleó siempre procedía de personas de la costa de Chile; es decir, eran como les he calificado bacilos extrangeros.

Ahora voy á tomar de los muchos estudios que se hicieron, algunos ejemplos de la marcha experimental de la tuberculosis contraída en La Paz.

Cobayo No. 1C.—Inoculado con esputo tuberculoso comprobado por examen microscópio, procedente de un individuo joven que había contraído la enfermedad en esta ciudad. Peso en el momento de la inoculación, 950 gramos. Fecha de la inoculación, julio 16, 1912; horas, 10 a. m.

Durante los primeros ocho días el animal no parece sufrir, pero desde esta fecha la temperatura se eleva, sobretodo en la tarde, llegando á 39° 4′ á 39° 5′; el apetito disminuye rápidamente, se presentan deposiciones diarreicas. El animal se queja y cuando se le toca la región abdominal, se comprueba un grado de sensibilidad excesiva.

El 8 de agosto el peso ha disminuído á 750 gramos. Muere el 18 del mismo mes, presentando el abdómen enormemente aumentado de volumen.

En la autopsia se constata en el peritoneo un derrame sero-purulento muy abundante y de mal olor; las paredes peritoneales están cubiertas, en toda su extensión, de una capa de peritonitis exudativa. Los intestinos repletos de gases se hallan bañados de un líquido purulento; en la gran curbadura del estómago se encuentra un foco de supuración que forma un verdadero absceso.

Examinados los diferentes exudados, se vé que encierran bacilo de Koch en gran abundancia.

Cobayo No. 2C (peso, 500 gramos).—Inoculado con esputo proveniente de un indígena de 15 años, hecha el 25 de julio de 1912. Hasta el 4 de agosto no se nota ninguna modificación apreciable, pero desde esta fecha la temperatura se eleva ligeramente en la tarde y el peso comienza á disminuir de manera que en agosto 12 sólo da 410 gramos. Muere el 18 de este mes. Á la autopsia se encuentran en el peritoneo abundantes granulaciones; el hígado aumentado de volumen está también sembrado de granulaciones, que le dan un aspecto grisáceo; los pulmones disminuídos de volumen, casi exangües, contienen numerosas granulaciones y hasta focos de degeneración.

Las dos experiencias anteriores, tomadas como las más importantes entre varias otras, nos dan la prueba de que es indudable que el bacilo tuberculoso indígena es mucho más virulento que el importado; pués, si se compara la primera, segunda y tercera série de experiencias, se vé que la primera y la segunda, en las que se ha empleado sea culturas puras ó esputos con bacilo extrangero, en todos ellos la curación se ha producido, en plazo más ó menos breve; mientras que las inoculaciones llevadas á cabo con esputos conteniendo bacilo indígena han producido la muerte en espacio de tiempo relativamente corto.

¿Cómo explicar este fenómeno? No quiero cansar la atención de esta ilustre asamblea, con la exposición de largas teorías, y es por esta razón que me voy á limitar á exponer en pocas palabras, cuál es en mi concepto la explicación del hecho observado.

Como ya en otro punto he dicho, yo creo que tanto las culturas como los esputos con bacilo extrangero no se encuentran aclimatados, de suerte que su acción es casi ineficiaz y, por otra parte, como pasa con todo organismo que no se encuentre en su verdadero médio, la reproducción es nula; de aquí es fácil deducir que debilitados los bacilos por una parte y no reproduciéndose por otra, la economía se encuentra en condiciones muy favorables, para reparar todos los daños causados por la enfermedad.

Cosa muy diferente pasa con el bacilo que ya ha tomado carta de ciudadanía en estas alturas; en este caso el bacilo está aclimatado, y como encuentra un terreno nuevo, es fácil también explicarse la razón de su particular virulencia.

La Paz, *Agosto de 1912.*

Temperaturas médias, máximas y mínimas, 1904.

Meses.	Media de máxima y mínima.	Media de las máximas.	Media de las mínimas
Enero	11.7	17.7	5.6
Febrero	12.7	20.2	5.2
Marzo	12.7	20.6	4.2
Abril	11.5	18.7	3.8

En junio la media máxima viene á ser 17.8; media mínima, 0.8.
En julio hemos tenido media máxima 15.5; media mínima, 3.8.

MILZBRAND UND SALVARSAN.

Dr. GEORG BECKER, Plauen i. Vogtland.

Von dem früher allgemein üblichen radikalen chirurgischen Vorgehen bei der Milzbrandpustel des Menschen ist man in letzter Jahren fast allseitig zurückgekommen. Zwar wird von einzelnen Forschern noch einem energischen aktiven Eingreifen das Wort geredet, so empfiehlt Barlach (Neumünster) eine kreisförmige Kauterisation um die Pustel und Jodeinspritzungen in der Umgebung. Gräf (Frankenhausen) frühzeitige Aetzung der Pustel mit dem Kalistift, doch ist die Exzision der Pustel weit im Gesunden, eventuell mit Ausräumung der regionären Lymphdrüsen wohl nur noch wenig in Anwendung. Auch im Hamburg-Eppendorfer Krankenhaus ist die früher geübte aktive Therapie seit 1896 verlassen worden zu gunsten eines streng konservativen Verhaltens mit Enthaltung von jeglichem Eingriff. Das seitdem bis zum November 1911 so behandelte Material von 60 Fällen ist von mir in den Mitteilungen aus dem Hamburgischen Staatskrankenanstalten, Bd. XIII, Heft 2. ausführlich veröffentlicht.

Bei der Bewertung der Therapie hat sich die bakteriologische Untersuchung des Blutes sehr bewährt.

Die Anwesenheit der Milzbrandbazillen im Blut ist leicht nachzuweisen, wenn man das mit einer Lüerschen Spritze aus der Armvene entnommene Blut direkt in verflüssigten und auf 40–45° abgekühlten Agar verimpft; auf den dann in Petrischalen ausgegossenen Nährböden entwickeln sich nach 12–24 stündigem Aufenthalt im Brutschrank die charakteristischen Kolonien.

Die in 45 Fällen vorgenommene bakteriologische Untersuchung des Blutes ergab in 12 Fällen ein positives Resultat. Es zeigte sich, dass in allen zum Tode gekommenen Fällen die Bazillen sich während des Lebens im Blut nachweisen liessen. Der früheste Zeitpunkt, in dem uns bei den tötlich endenden Fällen der Nachweis der Bazillen im lebenden Blut gelang, war 3 mal 24 Stunden vor dem Tode. In diesem frühen Zeitpunkte wurden in einem Fall 5 Kolonien auf 4 Platten zu 2 ccm, in einem anderen 20 Kolonien auf 6 Platten zu 2 ccm Blut gezüchtet. Bei der erst kürzere Zeit vor dem Tode angelegten Blutkultur war die Zahl der Bazillen wesentlich grösser, wenige Stunden vor dem Tode waren die Platten mit Kolonien übersät. Im Leichenblut liess sich regelmässig der Milzbrandbazillus durch die Kultur nachweisen.

Wenn wir vorerst die Fälle unberücksichtigt lassen, die mit einer Milzbrandbakteriämie in unsere Behandlung kamen, deren positiver Blutbefund also schon von vornherein eine schlechte Prognose gab, so erzielte die konservative Behandlung sehr gute Resultate. Unter

34 Fällen, deren Blutkultur bei der Aufnahme steril war, hatten wir nur einen Todesfall zu beklagen. Bei diesem, einem 28jährigen Gerber, sass die Milzbrandpustel an der linken Halsseite; es bestand ein sehr ausgebreitetes Oedem, doch war das Allgemeinbefinden kaum gestört, die Temperatur normal. Zwei Tage später erfolgte, wie die Blutkultur ergab, der Einbruch der Bazillen in die Blutbahn unter Fieber bis zu 40.8 und 168 Pulsen. Zwei weitere Tage danach erlag der Patient seiner Milzbrandsepsis. In diesem Falle, in dem die notwendige Ruhigstellung des Krankheitsherdes durch einen Verband wegen der Lokalisation am Hals nicht gut zu erreichen war und eine Ruhighaltung von dem Patienten wegen des fehlenden Krankheitsgefühls nicht beobachtet wurde, versagte die konservative Therapie. In allen übrigen Fällen, unter denen, wie aus der ausführlichen Veröffentlichung des Näheren zu ersehen ist, sehr schwere Erkrankungen mit weit ausgedehntem Oedem und schwer mitgenommenem Allgemeinbefinden waren, heilten die Kranken unter absoluter Ruhe und Analeptika, besonders Alkoholdarreichung.

Ganz anders gestaltete sich die Prognose der Kranken, in deren Blut sich die Bazillen bei der Aufnahme nachweisen liessen. Wir mussten die Prognose bei ihnen nach unseren Erfahrungen absolut infaust stellen und erst in jüngster Zeit haben sich uns auch für diese Fälle noch Heilungsmöglichkeiten ergeben in dem Salvarsan.

Ict habe zuerst das Salvarsan am 20. V. 1911 bei einem 55 jährigen Manne angewandt, bei dem aus 8 ccm. Blut 55 Kolonien gezüchtet wurden und der einen so schweren allgemein septischen Eindruck machte, dass er von allen Beobachtern für verloren angesehen wurde. Das Blut war an dem Tage nach der intravenösen Infusion von 0.6 Salvarsan steril, die Temperatur fiel 2 Tage danach zur Norm ab und der Kranke genas.

Dieser Fall schwerer Milzbrandbakteriämie ist bis jetzt der einzige durch Salvarsan geheilte geblieben. Wir hatten inzwischen nur noch bei zwei Fällen Gelegenheit, diese Therapie auszuwenden: in dem einen Falle war die in dem Blut vorhandene Bazillenmenge etwa 7 mal so gross wie in dem geheilten Falle, also etwa 50 Kolonien in 1 ccm., in dem anderen war das Blut schon überschwemmt mit Bazillen und die Infusion wurde an dem moribunden Patienten gemacht, in beiden Fällen ohne Erfolg. Trotzdem halte ich mich für berechtigt, diese eine Heilung einer schweren Milzbrandbakteriämie hier mitzuteilen, weil es durch das Tierexperiment gelungen ist, die Wirksamkeit des Salvarsans bei der Milzbrandinfektion darzutun.

Angeregt durch diesen Fall hat Herr Dr. Schuster in dem Stadtkrankenhaus Plauen i. V. Versuche an Kaninchen angestellt, die er mit einer 24stündigen auf Agarschrägröhrchen gewachsenen Reinkultur eines hochvirulenten Milzbrandstammes infizierte. Es zeigte sich, dass ein Kaninchen durch eine gleichzeitig mit der subkutanen

Milzbrandinfektion vorgenommenen intravenösen Salvarsaninfusion von 0.04 g. Kilo Tier gerettet wurde. Auch ein Tier, bei dem die Salvarsaninfusion 12 Stunden nach der subkutanen Milzbrandinfektion vorgenommen wurde, blieb am Leben und dauernd gesund. Auch bei einem intravenös mit Milzbrand infizierten Tier gelang es durch eine fast gleichzeitig (etwa 3 Minuten später) am anderen Ohr gemachten intravenösen Salvarsaninfusion das Tier zu retten, dagegen starben die erst nach 12,4 oder 1 Stunde mit Salvansan behandelten Tiere, nachdem ihnen die Milzbrandkultur in die Vene eingespritzt worden war. Bei einer Wiederholung dieser Versuche mit der halben Salvarsanmenge, also 0.02 g pro Kilo Tier starben alle Tiere an Milzbrandsepsis. Das Ergebnis dieser Versuche, die mit sicherem Ausschluss von Versuchsfehlern und bei Aufstellung aller Kontrollen angestellt wurden, ist also, dass Salvarsan in einer Menge von 0.04 g pro Kilo Tier imstande ist, Kaninchen mit sonst sicher tötlicher Milzbrandinfektion zu retten.

Unabhängig hiervon wurden zu derselben Zeit von Laubenheimer Tierversuche in gleichem Sinne angestellt. Er verwendete Meerschweinchen als Versuchstiere, die er subkutan infizierte und zwar mit 0.1 g. Salvarsan pro Kilo Tier, also mit wesentlich höherer Dosis wie Schuster. Die Resultate waren sehr ähnlich denen von Schuster: von den Tieren, die bis 20 Minuten nach der Infektion mit Salvarsan behandelt worden waren, starb nur eines an Milzbrand und auch dieses erst 22 Tage später als das Kontrolltier. Aber auch noch 6 Stunden nach der Infektion konnten bei einem Teil der Tiere durch die Salvarsaninjektion die in den Körper eingeführten Milzbrandkeime vollständig abgetötet werden. Wenn die Salvarsanbehandlung noch später, 16–22 Stunden nach der Infektion einsetzte, so war der tötliche Ausgang nicht mehr zu verhindern.

Der Ausfall dieser Tierexperimente macht es wahrscheinlich, dass der günstige Augang in meinem Fall schwerer Milzbrandbakteriämie dem Salvarsan zu danken ist. Es ist ausserordentlich schwer, über die Wirkung des Salvansans auf den menschlichen Milzbrand ein sicheres Urteil zu gewinnen. Denn beweisend für die Salvarsanwirkung sind nur die Fälle, in deren Blut die Bazillen nachgewiesen wurden, die anderen heilen, wie wir gesehen haben, auch bei Ruhigstellung. Die Dauer der Anwesenheit der Bazillen im Blut ist aber nur kurz, nach unseren Erfahrunge etwa drei Tage vor dem Tode. Von dieser Zeit kann für eine Heilwirkung des Salvarsans nur der Teil in Betracht kommen, in dem noch keine schrankenlose Vermehrung der Bazillen im Blut stattgefunden hat, indem also die in einem ccm. Blut gefundene Bazillenmenge gering ist. Ist dagegen die mit 1 ccm. Blut beschickte Kulturplatte mit Bazillen übersät, dann ist das Salvarsan unwirksam. Der Zeitraum im Verlauf einer Milzbranderkrankung, in dem die Salvarsananwendung einwandfrei als

Heilwirkung sich darstellt, ist also sehr kurz, es ist das Anfangsstadium der Bakteriämie. Um nicht missverstanden zu werden, möchte ich in aller Deutlichkeit aussprechen, dass ich bei dem Milzbrand, der immer die Gefahr einer Allgemeininfektion in sich schliesst und bei dem trotz fehlenden schweren Krankheitsgefühls schon eine Bakteriämie bestehen kann, unbedingt die sofortige Anwendung des Salvarsans empfehle, sobald der Kranke sich in unsere Behandlung begibt. Ein Beweis für die Heilwirkung des Salvarsans ist durch diese Fälle aber nicht erbracht, auch wenn wie es in beiden von Professor Bettmann (Heidelberg) mitgeteilten Fällen war, eine wesentliche Besserung nach der Injektion eintritt. Das subjektive Gefühl des Beobachters und sein allgemeiner Eindruck sind zu unsichere Kriterien bei der Entscheidung dieser Frage. Es wäre bedauerlich, wenn bei den Nachprüfugen über Salvarsanwirkung beim Milzbrand die Blutkultur nicht berücksichtigt würde, wie es in England 1905 geschah, als auf die Anregung Legges hin das Milzbrandserum vielfach Anwendung fand und jeder, der 2 oder 3 Fälle behandelt hatte, über seine Erfolge berichtete, ohne eine bakteriologische Kontrolle des Blutes vorgenommen zu haben. Es sollte, wo es möglich ist, zugleich mit der Salvarsaninfusion eine Blutentnahme zur bakteriologischen Untersuchung gemacht werden, nur so ist es möglich, mit Sicherheit festzustellen, ob dem Salvarsan wirklich eine Heilwirkung bei dem Milzbrande des Menschen zukommt.

Report of a Joint Session of Sections I and V on Poliomyelitis, will be found in Volume I, Part II.

Professor WILLIAM H. WELCH moved that an international commission be created, with Dr. A. Weber, of Berlin, as chairman, to standardize procedures for the study and differentiation of the typhoid-colon group, and to report at the next International Congress of Hygiene and Demography, and that this recommendation be transmitted to the Permanent International Commission for its approval. This motion was carried and was referred to the Permanent International Commission.

THE RELATION OF PARASITIC AMEBAE TO DISEASE.

By CHARLES F. CRAIG, M. D., Captain, Medical Corps, United States Army.
Washington, D. C.

INTRODUCTION.

Within the past seven years it has been definitely proven that the parasitic amebae of man, or entamebae, are divided into several distinct species, one of which is a harmless commensal; that all cultural amebae which have been thoroughly studied are free-living species having nothing in common with the parasitic species; and that the latter have not been cultivated.

These new developments in our knowledge of amebae necessitate a revision of some of our data connecting these organisms with disease in man, for all of the evidence gained by experiments on animals or man with cultural amebae must be discarded, as such evidence is of no value as showing the relation of parasitic amebae to disease in the human subject. In addition the results obtained experimentally in animals by feeding or injecting material containing entamebae must be revised in the light of the proven existence of a harmless and at least two pathogenic species.

CLASSIFICATION OF AMOEBAE.

In considering the relation of entamebae to disease in man it is necessary to have a clear understanding of the classification of amebae in general. Loesch placed the ameba he found in man in the genus *Amoeba*, calling it *Amoeba coli;* in 1879, or four years after the discovery of *Amoeba coli*, Leidy established the genus *Endamoeba* for the parasitic ameba of the cockroach, described by Butschli under the name *Amoeba blattae;* in 1897 Casagrandi and Barbagallo, after a thorough study of the amebae occurring in the intestine of man, became convinced that they differed both in morphology and life-cycle from those occurring free in nature and, apparently unaware of Leidy's genus *Endamoeba*, established for the human parasites the genus *Entamoeba*. While eventually it may be determined that the spelling of Leidy must be retained, I prefer at the present time to accept the name *Entamoeba* for the parasitic amebae, as this term has been accepted and is used by almost every writer upon the subject.

After the researches of Casagrandi and Barbagallo numerous attempts were made to separate the entamebae into distinct species, but it was not until 1903 that a clear description was given of at least two species of entameba occurring in man. During that year Schaudinn published his work upon parasitic amebae and differentiated two species—one a harmless parasite which he named *Entamoeba coli;* the other the cause of a form of dysentery, which he named

Entamoeba histolytica. I was able to confirm Schaudinn's work in 1905, and it has since been confirmed by many protozoologists in various parts of the world. Recently Prowazek found this species in dysentery cases in Samoa, and states that at no time in its cycle of development were cysts observed at all resembling those found in other parasitic species, but only the spore-like bodies described by Schaudinn.

A third species of entameba was described by Viereck in 1906. This parasite, which he named *Entamoeba tetragena*, occurred in cases of dysentery contracted in Africa, and his researches, as well as those of others, proved it to be a pathogenic species, and that it has a wide geographical distribution in the Tropics and subtropics, as well as in temperate climates. I have found this species in cases of dysentery contracted in the Philippines, Panama, and in New York, Illinois, Arkansas, and Wisconsin. At the present time some authorities believe that this species is identical with *Entamoeba histolytica*, but the point is far from proven, and until it can be shown that the process of reproduction by gemmation and spore formation, described by Schaudinn as characteristic of *Entamoeba histolytica* and confirmed by myself in many cases of dysentery, occurs also in *Entamoeba tetragena*, and that cases of *tetragena* infection occur which never present the characteristic four-nucleated cyst at any stage of the disease process, I am forced to consider the two species as distinct, despite the fact that the nuclear structure of *Entamoeba tetragena* during certain stages of development resembles very closely that of *Entamoeba histolytica.*

In addition to the three species mentioned, several others have been described in man, as *Entamoeba tropicalis*, Lesage; *Entamoeba minuta*, Elmassian; *Entamoeba nipponica*, Koidzumi; *Entamoeba williamsi*, Prowazek; *Entamoeba hartmanni*, Prowazek; and *Entamoeba polecki*, Prowazek. It is generally believed that most, if not all, of these species are founded upon insufficient data and that eventually they will be found to be identical with one or the other of the three species already mentioned.

It may therefore be stated that at the present time most authorities recognize three distinct species of entamoeba as parasitic in man, i. e., *Etamoeba coli*, *Entamoeba histolytica*, and *Entamoeba tetragena.* These species have been carefully studied by numerous investigators in many parts of the world and are based upon marked differences in morphology and in the reproductive cycle. The nuclear structure of each species is distinctive, while *Entamoeba coli* forms cysts containing eight daughter nuclei, this number being sometimes exceeded, *Entamoeba tetragena* cysts containing four daughter nuclei and *Entamoeba histolytica* cystlike bodies which are budded from the

parent organism. In all these species the differences in the method of reproduction have been carefully studied and, in my opinion, constitute the most important basis of specific differentiation.

The classification of the amebae that have been cultivated from the feces of dysenteric patients and from the pus of liver abscesses is in a most unsatisfactory condition. Several species and subspecies have been described by Whitmore, Walker, Williams, Werner, and others, but no agreement has been reached as to their exact specific status. For long regarded by Musgrave and Clegg, Walker, Lesage and Noc as true parasitic species, identical with the species of entamoeba which have already been mentioned, these cultivated amebae have been shown to be free-living species of the *limax* type by the more recent work of Hartmann, Werner, Whitmore, Walker, Liston and Martin, Wells, and the writer. All the cultural species that have been thoroughly studied contain a contractile vacuole, an organelle which is not present in any of the parasitic species of man, and they also differ greatly in their reproductive cycle. This subject will be referred to later in the discussion of the relation of these cultural species to disease.

RELATION OF ENTAMOEBAE TO DISEASE.

The following theories have been held regarding the relation of entamebae to disease in man: 1, that they are all harmless commensals; 2, that they are secondary factors in the etiology of disease: 3, that all species of amebae are capable of causing dysentery; and 4, that both pathogenic and nonpathogenic species are parasitic in man.

Recent researches have shown that the latter theory, i. e., that pathogenic and nonpathogenic species of entamebae are parasitic in man is correct. It is still impossible to say whether some other factor is necessary before the pathogenic species can cause disease but the evidence all points to the contrary opinion. At the present time it is generally accepted that certain species of entamebae are capable of producing dysentery, but a few authorities still maintain that these parasites are only secondary invaders of the tissues and are not responsible for the lesions present. In support of this contention they point to the fact that entamebae are found in many healthy individuals and in patients suffering from diseases other than dysentery; that dysentery occurs in epidemic and endemic form in regions where entamebae can not be demonstrated; that many different agents when injected into the intestine are capable of producing lesions like those of amebic dysentery; that direct infection of either animals or man with entamebae has never been proven; that the deductions based upon animal experiments are unsatisfactory; and that until we are able to cultivate the entamebae and to produce dysentery with pure

ultures we are not justified in claiming that they are the cause of he disease.

These objections, with the exception of the last mentioned, can all e answered by the results of work accomplished during the past ew years. We know that the presence of entamebae in health and n disease other than dysentery is explained by the occurrence of a listinct species which is nonpathogenic and which is a parasite of nan; that the occurrence of endemic and epidemic dysentery in regions where entamebae have not been demonstrated is due to the group of dysentery bacilli; that the lesions produced by the injection of either chemical or bacterial substances into the intestine are not identical with those produced by the entamebae; that direct infection of animals with entamebae has been abundantly proven, and that such experiments are reliable when properly controlled. As regards the last objection, i. e., that until pure cultures are obtained the causative relation of entamebae to disease can not be maintained, it may be stated that this is not a fair or valid objection, as there are other parasites well known to be the cause of specific infections which have not as yet been cultivated.

In support of the etiological relation of certain species of entamebae to dysentery we have the following facts: 1. The absolutely characteristic pathology of amebic dysentery and the constant presence of the pathogenic species of entamebae in the lesions and their absence from the lesions of other forms of dysentery; 2, the constant presence of pathogenic entamebae in the tissues of the peculiar form of liver abscess which ofter complicates amebic dysentery; 3, the production of typical amebic dysentery in susceptible animals by feeding and inoculation experiments with material containing the pathogenic entamebae and the demonstration of the parasites in the lesions so produced.

It is not necessary at this time to discuss in detail the pathology of amebic infection. It is a self-evident fact to all who have had experience with amebic dysentery at the autopsy table that the lesions of this disease are absolutely characteristic and are entirely distinct from those of the bacillary forms of the disease. I have had the opportunity of studying hundreds of cases of both amebic and bacillary dysentery at autopsy, and can state that one may easily distinguish the lesions produced by the entamebae from those due to other causes.

If sections are made through the lesions in the intestine, entamebae may be demonstrated in every portion of the involved region. They are frequently numerous in the mucous, submucous, and muscular coats of the intestine, where they may be demonstrated in the glandular tissue, in the intermuscular septa, and in the lymphatics and blood vessels. Of course, in the intestine, it can not be denied

that a portion of the pathological picture may be due to bacteria which have gained entrance to the tissues along with the entamebae but the fact remains that the latter organisms are always associated with a characteristic ulcerative lesion never produced by bacteria alone.

I believe that if we had no other evidence than the peculiar lesions of this form of dysentery with which are always associated the pathogenic species of entamebae we would be justified in considering the latter as the cause of the disease.

It is well known that a peculiar form of liver abscess frequently complicates amebic dysentery. The pathology of this condition is characteristic and in the contents of such abscesses entamebae can always be demonstrated and if sections are made of the abscess wall these organisms are found within the tissues. Frequently the abscess contents are sterile save for the entamebae, while the most careful staining of the tissues fails to reveal any other etiological factor.

The experimental production of dysentery in susceptible animals with entamebae dates back practically to the discovery of these parasites. Loesch produced the disease in a dog by the rectal injection of fecal material containing entamebae and his results were confirmed upon cats by Hlava, Kovacs, Kartulis, Zancoral, Strong, and Musgrave, and many others. Huber produced dysentery in dogs by feeding them feces containing entamebae and Kruse and Pasquale produced the disease in cats with the pus from an amebic liver abscess. The work of Harris, which has been largely overlooked by writers dealing with this question, was of great interest and importance. He endeavored to produce dysentery in dogs by the rectal injection of various bacteria and fecal material from dysentery cases. Among the bacteria injected were the typhoid bacillus, colon bacilli, anthrax bacilli, pyogenic cocci, the dysentery bacillus of Shiga and mixed cultures of bacteria from dysentery patients. His experiments were most carefully controlled and in not a single instance did the animals show any evidence of disease following the injection of the bacteria. On the other hand the injection of fresh feces containing entamebae in the rectum of puppies was followed in every case by a typical dysentery resulting in the death of the animal experimented upon. In two of the animals amebic abscess of the liver developed and entamebae were recovered from the abscess pus. In all of the animals, four in number, the lesions present in the intestine were typical of those found in amebic dysentery in man. The period of incubation varied from three to six days. Sections of the intestine of the infected animals exhibited the microscopic pathology of amebic dysentery and the entamebae were demonstrated in the tissues.

All the experimental work cited, while conclusive as to the production of dysentery in susceptible animals with material containing

entamebae, is inconclusive as regards the exact species used in the experiments, as these researches were made before Schaudinn's work in species differentiation. Since his observations, however, numerous investigators have proven that *Entamoebae coli* is not a pathogenic organism and that *Entamoebae histolytica* and *Entamoebae tetragena* are the species most frequently concerned in the etiology of amebic dysentery.

RELATION OF ENTAMOEBAE COLI TO DISEASE.

Entamoebae coli is a species frequently observed in the feces in both health and disease. Although it is probably world-wide in its geographical distribution the percentage of infection varies greatly in different localties, being highest in tropical countries and lowest in cold climates.

Schaudinn found it present in 50 per cent of healthy individuals in West Prussia, in 20 per cent in Berlin, and 66 per cent of healthy people examined on the shores of the Adriatic Sea; Vedder, in 50 per cent of healthy American soldiers, and 72 per cent of Filipino scouts in the Philippines; Sistrunk, in 11 of 145 patients suffering from diseases other than dysentery in the Mayo Hospital at Rochester, Minn, the patients coming from different parts of the United States; and Ashburn and the writer in 71 per cent of healthy American soldiers in Manila. In 1905 I examined over 200 American soldiers in San Francisco, who were recruited from different parts of the United States, and found that 65 per cent of them showed *Entamoeba coli* in the stools after a saline cathartic. This species has lately been demonstrated by Stiles in North Carolina, by McCarrison in India, and its occurrence in the Philippines confirmed by Whitmore and Walker. It has also been found upon the Isthmus of Panama by Darling and James, in South America by Elmassian, and in Samoa by V. Prowazek.

That this organism is not pathogenic has been proven by many investigators. Its common occurrence in healthy individuals, in whom it has been observed for months and even years without producing symptoms of diarrhea or dysentery, and the negative result of animal experiments by numerous investigators prove that this species is a harmless commensal of the human intestine. Negative results were obtained by Kartulis, Kruse and Pasquale, Celli and Fiocca, Strong and Musgrave, Kovacs, and Jürgens by injecting material containing entamebae parasitic in healthy individuals, and Schaudinn showed that this entameba, which he called *Entamoeba coli*, is capable of living in the intestine, but that it never produces symptoms of diarrhœa or dysentery either in animals or man.

I have made many attempts to produce dysentery in kittens with *Entamoeba coli*, both by injecting fecal material containing them into

the rectum and by feeding material containing both the encysted and vegetative forms, but have never been able to produce the least symptom of dysentery, although 50 per cent of the kittens given rectal injections of feces containing *Entamoeba histolytica* and 65 per cent of kittens fed with milk infected with material containing the same species developed severe dysentery.

In a recent personal communication Dr. Creighton Wellmann has furnished me with some data regarding experiments with *Entamoeba coli*. He infected five kittens by injecting 4 to 5 cubic centimeters of feces containing encysted *Entamoeba coli* into the rectum. All the animals remained perfectly well and were killed about one month after the injection. In none of them were any evidences of dysenteric lesions found at autopsy.

From the evidence which has accumulated it may be positively stated that *Entamoeba coli* is not a pathogenic parasite and that it has been found in a considerable proportion of healthy individuals in every region where it has been carefully searched for. This parasite is chiefly of importance because of the liability of confusing it with the pathogenic entamebae, and there can be no question that hundreds of cases of so-called amebic dysentery have really been diarrhœas due to other causes, but so diagnosed because of the finding of *Entamoeba coli* in the stools.

RELATION OF ENTAMOEBA HISTOLYTICA TO DISEASE.

I have already mentioned the numerous instances of the production of dysentery with material containing entamebae, but Schaudinn was the first to demonstrate the actual species concerned in many of these experiments. This species he named *Entamoeba histolytica* and he conclusively proved that it is the cause of a form of dysentery and that the so-called spores of this parasite are infective. He thus describes his experiments, which prove this point:

> From this case I took a small quantity of feces, divided it into three parts, dried each in the air, and mixed with it sufficient water for about 20 crude preparations under cover glasses. These preparations were carefully examined, the examination being conducted upon a mechanical stage and requiring many hours. No forms resembling the cysts of *Entamoeba coli* were found, but the small spores of *Entamoeba histolytica* were noticed in large numbers, but no vegetative organisms could be demonstrated. The cover glasses were then removed, the feces washed with distilled water, and ten such preparations were mixed with enough distilled water to form 1 cubic centimeter of the mixture. The feces of the animal to be experimented upon—a healthy, strong young cat—was carefully examined for amebae and none could be demonstrated. To this cat I gave the 1 cubic centimeter preparation mentioned above, mixing it with milk. On the evening of the third day the cat passed bloody mucoid feces and an examination showed the presence of great numbers of typical *Entamoeba histolytica*. In the afternoon of the fourth day the cat perished. Dissection

howed typical ulcerous dysentery of the large intestine and immigration of he amœbae into the epithelium could be easily established.

I will mention yet another experiment which goes to prove that the permaent spores by themselves are capable of producing a new infection. The feces f the cats developing dysentery contained only vegetative stages of the amebae, o spores being found. When large quantities of the feces were given to a cat t remained well and for four weeks showed no amebae in its feces. It was then ed with the remnant of the dried feces used in the first experiment, which contained multitudes of the spores, and after six days the amebae began to appear n the feces. Being older and larger than the other cat, it proved more resistnt to the infection and did not die until two weeks later. The autopsy showed he lesions of typical amebic dysentery.

Schaudinn's work served to explain the negative results of some observers with *Entamoeba histolytica*. During the active stage of dysentery only the vegetative forms of this species occur in the feces, and as these forms are not infective the experiments in which only material containing these forms are used will give negative results. However, if the feces from cases which are recovering from dysentery are used for experimental purposes a large proportion of susceptible animals will develop the disease, as at this stage of the disease the infective sporelike cysts are present.

In 1905 I was able to confirm Schaudinn's work regarding the pathogenic nature of *Entamoeba histolytica*. Half-grown kittens were used in my experiments, and 50 per cent of those given rectal injections developed the disease, while 66 per cent of the feeding experiments were successful. It will be noted that the latter method gave the best results, as 8 of the 12 kittens experimented with developed dysentery, *Entamoeba histolytica* being found in the feces and in sections of the diseased intestine. One of the animals developed an amebic abscess of the liver, and this species of entameba was found in the abscess contents as well as in sections of the abscess wall. The period of incubation varied from 6 to 14 days, being slightly shorter in the feeding experiments than after rectal injection.

All the kittens experimented upon were carefully examined for amebae prior to the experiments so as to rule out a previous infection. Both pure and mixed cultures of all bacteria that could be cultivated from the feces were fed and injected in order to control the tests, and in none of the kittens so treated did the symptoms of diarrhœa or dysentery develop, and at autopsy no lesions were found in the intestine.

In dysentery produced by the rectal injection of the infected material the lesions were usually localized in the rectum and were not so severe, as a rule, as when the infection was acquired through the mouth. The lesions produced were typical of those occurring in amebic dysentery in man and varied in extent and severity with the length of time the infection lasted. The symptoms consisted of

diarrhœa with the passage of blood-stained mucous stools, containing multitudes of motile *Entamoeba histolytica;* rapid emaciation with loss of appetite and strength; and finally death from exhaustion. In a few instances attacks of severe diarrhœa were followed by a period of constipation and the disease became chronic in nature. The longest period of incubation was 14 days in a kitten injected per rectum and the shortest period 6 days in an infection by the mouth.

The following protocols of autopsies will illustrate the lesions produced in kittens by *Entamoeba histolytica.*

Kitten No. 1.—This kitten was injected per rectum on October 15 and killed upon November 21, the first evidence of infection having appeared about October 30.

Kitten No. 2.—Body that of a half-grown kitten very greatly emaciated. The abdomen is greatly distended with gas. The mucous membrane of the anus appears swollen, and a considerable amount of blood-stained mucus is adherent to it. The subcutaneous fat has almost entirely disappeared and the muscles appeared dry and atrophied. The pleural cavities are free from fluid and the lungs appear normal. The heart is greatly congested and contains red clots in all the chambers. The liver is hypertrophied, deeply congested and marked albuminoid degeneration is present but there is no trace of abscess formation. The kidneys are congested and upon section present the usual lesions of an acute parenchymatous nephritis. The omentum contains a small amount of fat and is not inflamed. The bladder is filled with urine.

The intestines are greatly dilated with gas and fluid. Upon external examination the large intestine appears swollen, is grayish in color, with small, darker colored areas scattered along it. Upon opening the large intestine the mucous membrane of the rectum is found considerably swollen and inflamed, but no ulcerations are present. Above the rectum for a distance of about 10 centimeters the mucous membrane is very much swollen and edematous, bright red in color, and between the folds a considerable amount of pus can be seen. For a distance of about 4 centimeters from the upper end of the large intestine, the mucous membrane is inflamed, being red, swollen, and edematous. In this area there are numerous ulcerations covered in with bloody mucus; they are of small size, somewhat irregular in shape, and extend in most instances to the submucosa, although there are a few which extend to the muscular coat of the intestine; the edges are undermined and many of the ulcers are covered with necrotic tissue, brownish yellow in color, which has to be removed in order to expose them. A few of the ulcers communicate beneath the mucous membrane. The small intestine shows a rather severe acute enteritis and the stomach an acute gastritis.

Kitten No. 3.—This kitten was fed once with feces containing *Entamoeba histolytica*, and seven days later developed diarrhœa, the feces containing blood and mucus, as well as numerous motile amebae. At the end of two weeks it died, having presented severe symptoms of amebic dysentery during this time.

Autopsy: Body that of a half-grown kitten, very greatly emaciated. Subcutaneous fat entirely absent, and muscles dry and much atrophied. The abdominal cavity is free from fluid and the intestines appear normal externally. The pleural cavities are free from fluid and the heart and lungs appear normal. The liver is brownish red in color externally with irregular yellow mottlings. There is a small abscess present at the dome of the right lobe, measuring 0.25 centimeter in diameter, showing very distinctly through the capsule of the organ. Upon section of the liver the cut surface appears greatly congested, the lobules are distinct, and no abscesses are found other than the one mentioned. The gall bladder appears normal. The kidneys appear enlarged and congested and upon section show an acute congestion, with some thickening of the cortex. Externally the large intestine appeared slightly, if at all, congested, although the walls were markedly thickened. Upon opening the large intestine it was found filled with fecal material mixed with a large amount of pus and blood-stained mucus. About 1 centimeter from the anus, which was blood stained and covered with mucus, there was an area measuring 4 centimeters in length presenting the typical lesions of amebic dysentery as they are observed in man. The entire mucous membrane was swollen, congested, and edematous. Numerous nodular areas projected into the lumen of the intestine, which, when incised, were found filled with a glairy material containing hundreds of *Entamoeba histolytica*. There were also numerous ulcerations, more or less irregular in shape, with thickened and undermined edges; many were covered in with necrotic tissue, which, upon being removed, showed that the floor of the ulcer was formed by the muscular coat of the intestine. Many of these ulcers communicated with one another beneath the mucous membrane and most of them had penetrated to the muscular coat. The remainder of the large intestines presented numerous ulcerations typical of those seen in the intestine of patients who have died of amebic dysentery. The lesions were most marked just below the ileo-cecal valve, where large areas of the mucous membrane had been destroyed, the muscular coat of the intestine being exposed.

Kitten No. 5.—This kitten was fed with milk containing *Entamoeba histolytica* several times before dysentery developed. The period of incubation was eight days from the date of the last feeding, but from that time until it was killed, three weeks afterwards, the animal presented the symptoms of amebic dysentery, there being gradual loss

of appetite, emaciation, and a diarrheal discharge containing blood and mucus with numerous motile *Entamoeba histolytica*.

Autopsy: Body that of a half-grown kitten, much emaciated. Subcutaneous fat entirely absent and muscles much atrophied. The pleural cavities were free from fluid and the lungs and heart appeared normal save for congestion. Upon opening the abdominal cavity the small intestine appeared congested externally. The liver is hypertrophied and greatly congested. The kidneys are congested and enlarged and upon section showed the lesions of an acute parenchymatous nephritis. The large intestine was dark gray in color externally and was considerably thickened, especially toward the rectum. Upon opening the intestine it was found to contain much fecal material, mixed with blood, mucus, and pus. Commencing at the rectum and extending for about half the length of the large intestine, the mucous membrane was greatly swollen, bright red in color, and contained numerous ulcers. The majority of the ulcers were spherical in shape, the edges were undermined and greatly thickened, and many were covered in with necrotic tissue. Upon removing this necrotic material the base of the ulcer is found to be formed by the muscular coat of the intestine. The ulcers present were typical of the amebic ulcerations seen in the intestine of man in every respect. The remainder of the large intestine was black in color and gangrenous, the mucous membrane having been almost entirely destroyed, exposing the muscular coat throughout this portion of the intestine. About 4 centimeters below the ileocecal valve there was a small perforation measuring about one-sixth centimeter in diameter.

The following interesting cases of experimental infection with *Entamoeba histolytica* have been furnished me by Dr. Creighton Wellman. His data cover five kittens, of which four developed dysentery and one remained free from the disease.

Kitten No. 18.—On August 20, 1910, 4 to 5 cubic centimeters of feces containing the cysts of *Entamoeba histolytica* were injected per rectum. The kitten remained apparently healthly until September 1, when entamebae were found in the feces. From this time on the animal grew steadily worse and the number of entamebae increased. The animal was killed September 21, and the following conditions were found at autopsy: Great emaciation, heart and lungs normal, liver enlarged but with no abscesses. Kidney showed the signs of nephritis. The mucous membrane of the large intestine was inflamed and edematous, and there were numerous small ulcerations, scrapings from which showed many entamebae. The small intestine and the stomach appeared to be somewhat injected. Dr. Wellman stated: "I should call the condition found a typical amebic dysentery."

Kitten No. 19.—The same technique was employed in infecting this kitten. This animal developed dysentery and *Entamoeba histoly-*

tica was found in the feces. The autopsy record of this animal is not given.

Kitten No. 20.—This kitten was fed with 4 to 5 cubic centimeters of the same feces used in infecting the kittens already mentioned. After 8 days entamebae were found in the stools and the animal died on the fifteenth day after infection. The following conditions were found at autopsy: The kitten was much emaciated, heart and lungs normal, liver swollen and congested but showing no abscesses. The kidneys showed the evidences of nephritis. The mucous membrance of the entire large intestine showed typical amebic ulcerations, many of them burrowing in character. The scrapings from the ulcers showed numerous entamebae. The entire intestine appeared edematous.

Kitten No. 23.—This animal was fed with the same feces, and entamebae appeared in the stools on the ninth day after feeding. It was killed on the eighteenth day after infection and the same condition found as in kitten No. 20, but the lesions were not quite so severe.

Kitten No. 24.—This animal was fed with the same feces, but with negative results. No entamebae appeared in the feces and no lesions were found in the intestine when the kitten was killed on the twenty-eighth day after feeding. This animal was considerably older than the others experimented with, and I have found that for successful results young kittens must be used, as full-grown cats are much more resistant to amebic infection.

Wellman states in his letter that he considers the lesions produced experimentally in these kittens as identical with those of amebic dysentery in man. More recently Werner, working at the Sailor's Hospital, in Hamburg, has produced dysentery in cats with *Entamoeba histolytica.*

He experimented with two strains of *Entamoeba histolytica*, only one of which he found infective. He was able to produce dysentery in cats with this strain, but found that after six passages the organism lost its virulence. The incubation period varied from 4 to 13 days, the average being 9 days. Of six cats infected with this species four died, the duration of the disease varying from 7 to 24 days, the average being 15 days. The animals were infected per rectum. Werner states that the lesions were typical of amebic dysentery and were always confined to the colon, especially the lower portion. Guinea pigs and rats were found to be resistant to infection with this parasite.

From the evidence which has been submitted I believe it is impossible to conclude otherwise than that *Entamoeba histolytica* is the cause of a form of amebic dysentery. The character of the lesions present in this condition, the constant association of this species with

the lesions, and the production of similar lesions in susceptible anim with material containing *Entamoeba histolytica* I consider conclu proof that this parasite is a cause of amebic dysentery in man.

RELATION OF ENTAMOEBA TETRAGENA TO DISEASE.

The experiments of Viereck, Hartmann, and Werner prove th this species produces a form of dysentery, although Hartmann b lieves that it is not as pathogenic to cats as *Entamoeba histolyti* The incubation period in his experiments varied from 8 to 10 da and the infection lasted from 3 weeks to a month. He states that a autopsy the cats presented the typical lesions of amebic dysentery s observed in man and that *Entamoeba tetragena* was found in t tissues.

Werner experimented with 5 strains of *Entamoeba tetragena*, o 8 of which were found to be pathogenic. One of these was still i fective after 5, one after 3, and one after 1 passage through ca but they all lost their virulence after repeated passage. The inc bation period in his animals varied from 5 to 12 days, and th disease lasted from 3 to 25 days, the average being 17 days. H states that he did not find any marked differences between the lesio produced by *tetragena* and *histolytica* and that he does not beli that the evidence supports the idea that one is less pathogenic th the other.

Werner describes an interesting experimental case in which a ca infected per rectum with a strain of *tetragena* developed dysente after 5 days incubation, the stools containing many entamebae. A the end of 12 days the animal died and at autopsy typical amebi ulcers were found in the lower portion of the colon, while the rig lobe of the liver showed an abscess the size of a hazel nut upon th anterior surface. The pus from the abscess contained entameb of the *tetragena* type.

Franchini reports the production of dysentery in a monkey b rectal injections of fecal material containing *Entamoeba tetragen* The monkey experimented upon had been under observation in th laboratory for over a year, was perfectly healthy, and repeate examinations of the feces before the experiment showed them to b free from entamebae. After the rectal injections of material co taining *Entamoeba tetragena* the animal developed an intense dysen tery, the stools containing blood, mucous, and multitudes of en tamebae identical in morphology with those injected. The anim died from the infection and at autopsy ulcers were found in th large intestine and *Entamoeba tetragena* was demonstrated in section of the diseased tissues.

In a personal communication Dr. H. B. Fantham states that h was successful in producing dysentery in one of two kittens fed upo

feces containing *Entamoeba tetragena* from an infection contracted in Algeria. The kitten died in 3 weeks, and ulcerations were found in the intestine which contained *Entamoeba tetragena*. His experiments in kittens with rectal injections of material containing this parasite were all negative.

I have had no personal experience with the experimental production of dysentery in animals with this species, but I consider the evidence sufficient to prove that it is capable of causing the disease in susceptible animals and that it is a very frequent cause of dysentery in man. I have found *Entamoeba tetragena* in patients suffering from dysentery contracted in the Philippine Islands, Panama, and several of the United States.

RELATION OF CULTURAL AMOEBAE TO DISEASE.

As several authorities have reported instances of the production of dysentery in animals with cultures of amebae it is necessary to consider briefly this phase of our subject. I have already stated that it has been proven by numerous investigators that all cultural amebae, that have been thoroughly studied, belong to the genus *Amoeba* and differ in morphology and life cycle from the parasitic species belonging to the genus *Entamoeba*, and that there is no sufficient proof that any of the latter species have been cultivated.

Prior to the work of Musgrave and Clegg several authorities claimed to have produced dysentery in cats with cultures of amebae, while others were unsuccessful in thus producing the disease. It is unnecessary to consider here the conflicting results obtained by such investigators as Kartulis, Vivaldi, Cassagrandi and Barbagallo, and Zaubitzer along this line, but the work of Musgrave and Clegg deserves special consideration. These authors were successful in cultivating numerous strains of amebae in symbiosis with bacteria from the feces of dysenteric patients and from liver abscess pus. They refused to accept the classification of Schaudinn and considered that all amebae might, under certain circumstances, become pathogenic. They were successful in producing ulcerations of the intestine and liver abscess in monkeys with mixed cultures of their amebae and various bacteria, and in one instance they claim to have produced amebic dysentery in man with a pure mixed culture of amebae isolated from the stools of a dysenteric patient.

In the light of our present knowledge these experiments of Musgrave and Clegg have no value as showing the relation of entamebae to disease. The work of Hartmann, Werner, Whitmore, Walker, and the writer has proven conclusively that the amebae cultivated by these authors are not entamebae but free-living amebae, and the species with which Musgrave and Clegg claim to have produced

dysentery in man is a typical free-living ameba of the *limax* typ The occurrence of dysentery after the administration of this cultu can be explained in many ways: The culture may have become i fected with the cysts of *tetragena* or *histolytica*, or the man ha become naturally infected or have been infected at the time of th experiment, for in a region such as Manila natural infections wou be very difficult to guard against. As regards the lesions produc in monkeys with cultures of amebae it should be remembered tha these animals suffer naturally from amebic infection, and there i no evidence in the authors' papers that repeated examinations o the animals' stools were made for a sufficient period of time befo the experiments to prove their freedom from entamebae.

The occurrence of dysentery in monkeys after feeding or injecting cultural amebae is probably explained, in the vast majority o instances, by the fact that at least two species of entameba ar parasitic in monkeys, as shown by Castellani and v. Prowazek, an that these species are capable of producing dysentery in these ani mals. Greig and Wells have also shown that in India natura amebic infection in monkeys is very common; thus every one of 5 monkeys with which they desired to experiment showed amebae i the feces which resembled those found in man. These organism only appeared at irregular intervals, so that repeated examination of the feces were necessary in order to demonstrate them. Some o the animals presented symptoms of dysentery while under observa tion, while others appeared perfectly healthy. I do not know th percentage of monkeys infected with entamebae in the Philippines but I personally observed three naturally acquired amebic infec tions in these animals in Manila, and I have no doubt that carefu examinations, covering a sufficient period of time, would demonstrat that a considerable percentage of monkeys in these islands harbo entamebae which could easily be confused with those parasitic in man.

In many of their experiments (Musgrave and Cleggs) the amebae were grown in symbosis with the typhoid bacillus, and this mixed culture was injected directly into the liver subcutaneous tissue, or the abdominal cavity of the animals used, and was followed by the appearance of abscesses containing both amebae and bacteria. It is well known that the typhoid bacillus is capable of producing abscesses when thus injected, and I have observed the formation of abscess of the liver after the injection of pure cultures of this organ ism into the organ, so that deductions based upon such experiments are valueless as proving the pathogenicity of any ameba. Even though lesions were produced in animals with these cultures of amebae they would bear no relation to the disease as it occurs in man, because the cultivated amebae are entirely distinct from the true

parasitic amebae which cause dysentery in man. Personally I believe that some of the lesions described by Musgrave and Clegg were produced by the mixed cultures of amebae and bacteria, with which they worked, but I can not admit that the cultural amebae are identical with the parasitic species, or that their experiments are of any value as showing the relation of entamebae to disease.

The claim of Musgrave and Clegg that the differences in structure and life cycle of the cultural amebae are due to artificial surroundings can not be accepted. Walker, in discussing this argument, very justly says: "That while slight modifications might occur under such conditions, it is very improbable that cultivation could cause a complete reorganization of the structure of the nucleus, develop de novo such a constant organelle as a contractile vacuole, or profoundly modify the life cycle of the organisms. Moreover, that the supposed modification should invariably take the form of a change from the characters of the genus *Entamoeba* to those of the genus *Ameba* is, to say the least, improbable."

It is not difficult to explain the ocurrence of free-living amebae in cultures made from feces, liver abscess pus, or from the intestine at autopsy, if one remembers that the cysts of these species are present in the atmosphere, and may thus easily contaminate the cultural material. The recent observations of Liston and Wells prove that it is possible to secure cultures of free-living species of amebae upon media exposed to the air, the organisms in such cultures agreeing in morphology with those obtained in cultures from the feces and intestine. Though it is possible for the free-living species to pass through the intestinal canal of animals in an encysted state and afterwards develop in cultures, it should be remembered that unless the most careful cultural technic is used such amebae may contaminate the cultures from the atmosphere, and it is probable that this is the manner in which many cultures have been obtained, especially in regions where the free-living species are found abundantly. However, it is very difficult to understand how anyone possessing accurate knowledge of the morphology and life history of amebae could mistake these cultural species for any of the entamebae of man.

CONCLUSIONS.

The following conclusions appear to be justified as regards the relation of entamebae to disease.

1. *Entamoeba coli* is a harmless commensal in the human intestine.

2. *Entamoeba histolytica* and *Entamoeba tetragena* are pathogenic species capable of producing in man the disease known as amebic dysentery.

3. *Entamoeba coli*, *Entamoeba histolytica*, and *Entamoeba tetragena* are strictly parasitic species and have not been cultivated.

4. There is not sufficient evidence at present to prove that any of the ameba that have been cultivated are pathogenic to man. All cultivated species belong to the genus *Amoeba* and differ greatly in morphology and life cycle from the parasitic ameba, which belong to the genus *Entamoeba*.

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THE IDENTIFICATION OF THE PATHOGENIC ENTAMOEBA OF PANAMA.

Dr. S. T. DARLING, Chief of Laboratory, Isthmian Canal Commission, Ancon, Canal Zone.

The identification of the entamoeba that causes dysentery and liver abscess in Panama has recently been placed on a satisfactory basis since two of the members of the hospital staff have given special attention to the subject, and have had referred to them for diagnosis all cases of entamoebic dysentery. Formerly, each doctor diagnosed the cases in his own ward, and there was no uniformity in the identification of entamoebae, each man determining for himself whether in a given case the entamoeba was *E. coli* or *E. histolytica*.

Influenced by the work of Schaudinn and Craig, until a year ago I regarded all pathogenic forms as *E. histolytica*. In August, 1911, a careful study of the entamoebae found in clinical cases of entamoebic dysentery and entamoebic liver abscess was begun, and observations since then have led me to be of the opinion that the only pathogenic form in this region is *E. tetragena* (Viereck.).

Having ample facilities for the collection of material from clinical cases, autopsies and the operating room, and for animal experimentation attempts were made to determine the specific characters of the entamoebae so collected.

Methods of examination:

1. Fresh and moist-chamber preparations, and those stained intravitam with gentian violet.

2. Wet-fixed preparations, stained with haematoxylin, Romonowsky modifications, and various other stains.

3. Dry-fixed preparations, stained by modifications of the Romonowsky method.

4. Animal inoculations and feeding experiments.

Examination of fresh preparations:

It was found that very few of the published descriptions of entamoebae were sufficiently helpful as guides for the purposes of identification; in fact, every step required to be specially worked out, and clinical and morphological data correlated with animal experimentation.

Take the questions of refractility of the ectoplasm and the color of the cytoplasm. It seems to me that refractility is very largely a question of the age of the entamoeba, or its relation to encystment, without regard to species. I have found, in cultures of free living forms, that the younger amoebae were not very refractile, while those approaching the period of encystment were quite refractile. In a fatal case I found that large trophozoites deep in the submucosa in the floors of ulcers were very slightly refractile, while many of the smaller entamoebae, in the more superficial sloughs, were highly refractile, yet they were representatives of one species. In some clinical cases all the forms seen were highly refractile, many contained chromidia, and were the precursors of the small generation from which the cysts develop. In other cases all the entamoebae were finely granular, contained no erythrocytes, and were not refractile. I have never seen, either with natural or artificial illumination, the green or gray tints noted by several writers, and it does not seem to me that stained specimens bear out the notion that green color is due to lysed erythrocytes, for the latter are held intact for a considerable period in the endoplasm, and disappear by condensation and erosion, while retaining their staining characters. I should say that all observations were made with artificial light, transmitted through blue glass, and I wish to call attention to the necessity of using some such uniform method of illumination, for the difference in illumination between light derived from a blue sky, or from white clouds, makes their use as sources of light uncertain, and gives inconstant pictures usually not noted by the observer. The resulting errors may be eliminated by the use of artificial light.

The nucleus is said to be inconspicuous in the pathogenic entamoeba in fresh preparations, but I have not always found this to be the case when artificial light has been used. It is true that in many individuals, or in all the individuals in some cases, the nucleus can not be made out in fresh preparations. But when one learns to recognize the nucleus nothing within the trophozoite is more conspicuous. The refractile granules or masses of peripheral chromatin stand out with great prominence and may be followed with ease as the entamoeba moves.

The presence of an ectosarc is very constant in the trophozoites of the pathogenic form, and is an important feature for differentiation from *E. coli*.

While, in most cases, it is true that all entamoebae detected in stools associated with pus blood and mucus are pathogenic, it is not this type of case that presents difficulties. The puzzling cases are those in which entamoebae are detected in fluid stools containing mucus, or in semisolid or formed stools unassociated with blood or pus, but

which it is necessary to diagnose at once, so that treatment may be started energetically.

METHODS OF STAINING.

As an aid to rapid diagnosis, I have used, with some success, gentian violet as an intravitam stain. The stain is used in the concentrated fluid form, or diluted with an equal amount of water, and is either added to the flake or mucus or drawn under the cover slip and the preparation examined immediately. While many individuals become overstained or remain understained, usually they will gradually take up the stain in such a manner that the peripheral chromatin, the centriole and karysome in *E. tetragena* stand out with almost the clearness and definition of well-stained hematoxylin preparations fixed in the wet way, and differentiation from *E. coli* is easy. I have tried several basic stains, but none is so good as gentian violet for intravitam staining. Even when the trophozoite is very refractory to the stain, as in the small generation and in the forms which contain chromidia, the nucleus for some reason will become more refractile and conspicuous. The nonrefractile trophozoites take up the gentian violet rapidly, while cysts and the refractile forms take up the stain slowly.

Haematoxylin-stained preparations were made from those fresh films which contained a sufficient number of entamoebae to warrant staining and study. The cover slip was removed, and both slip and slide were fixed in Schaudinn's bichloride alcohol, or in Zenker's solution diluted one-fourth and one-eighth, as the full-strength solution causes artefacts in the nucleus. Several haematoxylin stains were used and particularly clear pictures were obtained with Mallory's phosphotungstic acid haematoxylin, with the modification that the films were not given a preliminary treatment with oxalic acid or permanganate, but were placed over night in the haematoxylin, and then differentiated with very dilute permanganate. This is a shorter way of using phosphotungstic acid haematoxylin, and gives excellent results.

Fresh and wet-fixed preparations were controlled or compared with others stained after dry fixation by some modification of the Romanowsky stain. The films were thoroughly dried, then stained with Hasting's stain, overstained with Giemsa's stain, and differentiated with ammoniated alcohol. It was observed that the descriptions of pathogenic entamoebae, as well as figures used to illustrate them in the literature, did not correspond with the results obtained in well-differentiated films stained by the method just described. And it is believed that descriptions in the literature based on films stained in the usual way that had not been sufficiently differentiated are not as exact as they might be. Romanowsky stains

ve a tendency to overstain, just as haematoxylin does, though not intensely as the latter, and this overstaining must be corrected the use of a differentiating agent.

It has been my practice to stain in the following way: Fresh cover-p preparations containing a sufficient number of entamoebae to arrant staining and study, or those intended for diagnosis, are made to smears by sliding off the cover slip and thoroughly drying both ip and slide, after which each is stained with Hasting's stain for 15 inutes. Satisfactory films are then overstained with Giemsa's stain ıtil the film has a diffuse reddish purple tint. The film is then lunged into 60 per cent ethyl alcohol containing about 1 per cent of ater of ammonia (10 per cent), and differentiated in this, washed ı water, and controlled by the microscope until the purple substance f the nucleus and the blue color of the cytoplasm are strongly con-rasted. The film when properly differentiated has a blue violet olor. If the film has been greatly overstained, it is treated with a ıomentary douche of 95 per cent alcohol. Beautiful pictures are btained in this way, but, what is of more importance, the various gures displayed by the purple staining substance (karyosome?) an be noted and followed with ease. This purple staining sub-tance, in the nucleus of *Entamoeba tetragena* in dried-fixed films, epresents only a portion of the nucleus, as the centriole and periph-ıral chromatin do not stain purple by the above method. The pur-ple staining substance in the nucleus of *E. tetragena* frequently ıppears as a ring, or as a reticulum, or scattered granules. Its phases lo not appear to have been accurately described, but have been con-fused with the appearances presented in wet-fixed films when basic stains have been used.

Here I wish to call attention to certain errors of interpretation which I believe have resulted from the failure to properly distin-guish between the purple staining substance, or karyosome of the nucleus in *Entamoeba tetragena* in dry-fixed films, and the nuclear substance which stains with basic stains in wet-fixed preparations. For example: cuts showing the purple chromation of the nucleus of *E. histolytica* represented by Craig and illustrated in its proper color, have been used by other writers and figured in terms of haematoxylin, or black and white, without explaining that the black in the figure represents the purple staining substance of dry-fixed Romanowsky preparations. Dry-fixed stained films should never be confused with those stained after wet fixation, for the pictures are different in each case, and the mistake should never be made of attempting to trans-late one into the other. In dry-fixed films the permeability of the entamoebae to stains apparently has been profoundly modified, for the centriole and the peripheral chromatin do not take or retain the

purple stain. The karyosome alone retains the purple stain, while the remainder of the nucleus stains faintly blue, sometimes revealing the achromatic granules of uniform size which appear to form part of its structure.

Feeding and inoculation experiments:

A number of kittens, cats, dogs, and monkeys have been fed by mouth, or inoculated per rectum, with cysts and trophozoites of *Entamoeba tetragena*. When tetragena cysts have been fed to half-grown cats, there has resulted, not the typical entamoebic [1] colitis such as is usually described in the literature, but an enteritis, and in this lesion in the ileum, trophozoites have been found which, though arising from tetragena cysts, had the morphology not only of *E. tetragena*, but of *E. histolytica* and *E. nipponica*. Now, as material which, from its history and microscopical appearance, was certainly a pure culture of *E. tetragena* cysts was used in the experiment, and as the various forms appeared in the cat's intestines, I am led to believe that the large vegetative trophozoites, described as *E. histolytica* and *E. nipponica* by various writers, are nothing more than the large trophozoites in the first place, and atypical or degenerate form of *E. tetragena* in the latter, and I am confirmed in this opinion by never finding in my cases any of the perpetuating forms described by Schaudinn and Craig for *E. histolytica*. In one fatal case of tetragena infection, I observed from autopsy material many trophozoites that protruded psudopodia not unlike those figured by Craig for *E. histolytica*. Their extremities were refractile and appeared to contain a round, spore-like body; yet when these coverslip preparations were fixed immediately and stained with haematoxylin and by Romanowsky, the picture presented was that of *E. tetragena*, and the spore-like bodies had disappeared. In studying a strain of *E. tetragena* in cats, following rectal injection of trophozoites, I found at the fourth remove in dry fixed preparations a great many trophozoites, the peripheries of which contained one or several labose projections, which were very frequently deeply stained blue or contained a nucleus and suggested strongly the descriptions of *E. histolytica* by Craig, but these were artefacts; for, in wet-fixed haematoxylin preparations from the same coverslip preparation, the picture was that of *E. tetragena;* and associated with these trophozoites were several uninucleated tetragena cysts. If only the dry-fixed films had been studied in this case, they might easily have been described as *E. histolytica*.

With reference to rectal inoculation of trophozoites, infection occurs within a few days (5 to 8) if the strain is not too aged or near the stage of encystment; while, by mouth feeding, the duration is longer (12 days). In this, my experiments have not paralleled those of other writers. It is difficult to explain this; but I may

ay that, after several unsuccessful attempts to infect very young kittens and adult cats, I subsequently only used kittens weighing about 700 grams.

Animal experimentation is of very great value in studying the variation in a given strain. In a strain in kittens recently, I have been able to watch senility gradually developing from week to week, the entamoebae becoming reduced in size, filled with chromidia, and ultimately becoming encysted.

The comparative study of staining and fixing agents has brought out some very interesting information. The very marked differences presented by dry-fixed and wet-fixed stained preparations have been referred to. Phosphotungstic acid haematoxylin gives varying pictures, depending on the fixative. More information of the structure of the nucleus is obtained by the use of this stain, after fixing with diluted Zenker's fluid (one-eighth and one-fourth) and Flemming's fluid. The karyosome is not so well transfixed when fixed with Merkel's, Hermann's, or Schaudinn's fluid. In wet-fixed films stained by Romanowsky, it was never possible to stain the trophozoites exactly like the tissue cells near by. When stained by Giemsa's method, and differentiated in acetone xylol, the peripheral chromatin usually stained blue, while the centriole and nuclear sap stained pink or red, the tissue cells nearby displayed purple staining substance throughout the nucleus.

It was possible, in several cases, to study first the tissue destroying trophozoites, later the small generation, and, finally, during convalescence and after apparent recovery, the cysts, although in practically all cases that received energetic medication, the small generation and cysts did not appear.

The detection of crysts in convalescent and recovered cases is most important, for it is the cyst and not the trophozoite which is the infecting agent and makes the host of the former a "carrier." The identification of tetragena cysts is usually easy in stained preparations, and should present no difficulties in fresh films, yet the cysts are so small (12 to 15 microns in diameter) that they have frequently been mistaken for monad or coli cysts, or fat droplets, or possibly mononuclear leukocytes. When in doubt, and when the number of cysts was too small to risk loss by fixation and staining, I have vaselined the preparation, or kept it in a moist chamber; and, if the cyst was homogeneous at first, after one or two days, one, two, or four nuclei became distinctly visible. Tetragena cysts are more commonly detected in neglected cases which have partly recovered from entamoebic dysentery who may have diarrhoea or whose stools are solid; and I have found cysts in a case that had been insufficiently treated by means of rectal injections. It would seem that if a case of dysentery is treated early and energetically, the tropho-

zoites are at once driven from the field, leaving none to develop the drug-resistant small generation from which the cysts arise. T it will be seen is analogous to the rational treatment of malaria which the asexual generation is destroyed at once by large dose quinine, thus destroying all the forms from which the gametes ar

In acute or new infections, or in very active lesions, many of t trophozoites are of large size—30 to 60 microns in diameter. As t strain grows older, it often becomes reduced in size, the trophozoi measuring from 12 to 24 microns in diameter. These forms fr quently contain coarse blocks of chromidia, and they constitute t "small generation." During convalescence, and after appare recovery, there appear small trophozoites, 12 to 15 microns in dia eter, and associated with them are cysts and four nucleated schizon If relapse occurs with symptoms of colitis, large trophozoites ma their appearance again, and the cysts will have disappeared. Th during the progress of a case of tetragena dysentery, one will see first large trophozoites, many or all of them having the charac described for *E. histolytica* by Schaudinn and Craig, and one w see later, if the case has been a neglected one, the small generati with cysts, of which there is no better description extant than th in Elmassian's paper on this form, which he has called *E. minuta*

If there is a sufficient number of cysts, they may be fed by mou to young cats, and it may be possible to recover from their bow lesions trophozoites having not only the characters of *E. tetrage* but of *E. histolytica* and *E. nipponica* as well. Or, if in an given case of tetragena dysentery, in which the trophozoites are o the histolytica type, they be injected rectally into a young cat, an the strain carried on by subsequent rectal inoculation into other ca at the time the infected animal dies, so as to prolong the vegetati phase of division, then it will be seen that the histolytica-like troph zoites become reduced in size, filled with chromidia, and, at th fourth or fifth remove, it is possible to find uninucleated tetrage cysts. The nucleus of the trophozoite meanwhile has taken on typical tetragena appearance with a prominent karyosome. It now impossible to infect other cats per rectum with this material. I we make dry-fixed Romanowsky-stained smears of material con taining these typical tetragena trophozoites, they will occasionall present the morphological peculiarities of *E. histolytica* describe by Craig, and we are thus able to correlate most of the observation of Schaudinn, Craig, Elmassian, and Koidzumi, and state that ther is almost certainly but one pathogenic entamoeba, and that one i *E. tetragena.*

[1] Since reading the paper (December 9), I have provoked entamoebic colitis in a kitten fed with tetragena cysts that had been in the moist chamber 5 hours.

DISCUSSION.

Prof. CREIGHTON WELLMAN, New Orleans: I may add to the refer-ıce to my animal experiments made in Capt. Craig's paper that since ıe data sent him I have made a few more feeding and rectal injec-on experiments in kittens, using both what we regard as *coli* and *istolytica*. The protocols of these run about as those sent him, no sions resulting from *coli* and frequently following *histolytica* infec-ons. Perhaps I ought to add that the animals employed were care-ully and repeatedly examined for some time before the experiments ere begun.

Capt. CHARLES F. CRAIG, Medical Corps, United States Army: I ıave been much interested in the valuable paper of Dr. Darling egarding the species of entamoeba producing dysentery in Panama. Dr. Darling believes, from his observations, that *Entamoeba tetra-ena* is the only pathogenic amoebae present there, but I have found what I believe to be *Entamoeba histolytica*, as well as *Entamoeba tetragena*, in properly stained preparations sent me by Dr. James for my opinion. As I have stated in my paper, until it can be shown that the peculiar method of reproduction described by Schaudinn as budding or gemmation, and afterward confirmed by myself in both living and stained entamoeba, occurs in *Entamoeba tetragena* as well as *Entamoeba histolytica*, I must consider the two as distinct species, despite the fact that at certain stages of development the nuclear structure of *tetragena* resembles that of *histolytica*. Though there is a resemblance, I will say that I have seen Dr. Darling's preparations, and even in those entamoeba presenting the *histolytica* type of nucleus, the centriole is much larger and the nuclear membrane much thicker than in the true *histolytica*. As regards the spores described by Schaudinn and myself and others being artefacts, I would say that I am sure that such a mistake could not be made, especially when we both observed the process in the living parasite. I am quite sure that I know artefacts when I see them, and I am still more sure that Schaudinn did. This supposition proves, to my mind, that Dr. Darling has not handled *histolytica*, or, if so, has failed to recognize the species, for no one could mistake the *histolytica* spores for artefacts. They are small, oval bodies, measuring on the average about 4 microns in diameter, somewhat bile stained, and having a single or double contoured membrane, and they may be very easily overlooked by one who has not once had then pointed out. They show no structure on staining because of the deepness of the staining and the impossibility of extracting the stain.

Specimens of both *histolytica* and *tetragena* frequently occur in the same case, and this does not appear to be considered by Dr. Darling in his paper. I have repeatedly seen mixed infections with these two species, as well as single infections.

The process of cyst formation in *Entamoeba tetragena* is distinctive, four nucleated cysts being produced, but such cysts *never* occur in the developmental cycle of *histolytica*. I have followed scores of cases of pure *histolytica* infection through every stage of the disease, from the acute attack until recovery appeared complete, and through several relapses, and have never observed a single *tetragena* cyst, the only forms being the minute spores which are found during healing and apparent recovery. Dr. Darling states that in his cases showing amoebae having the *histolytica* type of nucleus cysts are observed when the patient improves. In this case he may have been handling a mixed infection with *histolytica* and *tetragena*, or the amoebae were all *tetragena*, some of them showing a nucleus resembling *histolytica*, but which, as I have already said, is not identical with the true *histolytica* nucleus. In addition, Dr. James, one of Dr. Darling's colleagues on the Isthmus, in a letter received by me only a day or two ago, states positively that the infections he regards as being due to *histolytica* do not show four nucleated cysts at any time in their course, and that in addition the clinical symptoms of *histolytica* infections are different from those of *tetragen* infections.

As regards the examination of entamoeba by natural and artificial light, I would say that I am familiar with the appearance of the organisms under both methods of illumination, but daylight is certainly preferable in work with these parasites, provided the light comes from the north. The nucleus of *histolytica* very frequently is invisible in the living parasite, no matter what method of illumination is used.

In his paper Dr. Darling states that he was not able to produce the typical lesions of dysentery in the colon of kittens with *Entamoeba tetragena*, but instead a severe enteritis, the condition being most marked in the ileum. This is a totally different result than is obtained with experimental infections with *Entamoeba histolytica*, in which the lesions are typical and almost always confined to the large intestine, very seldom being marked much above the ileo-caecal valve. These observations of Darling would apparently show that the lesions in cats produced by *tetragena* differ very markedly from those produced by *histolytica*.

The presence of four nuclei in the vegetative stage of *tetragena*, noted by Dr. Darling, is most interesting, as the process of schizogony has not been definitely proved in this species, and these observations would appear to prove that it occurs.

Dr. Darling's remarks concerning the morphological differences in tamoebae, caused by dry and wet fixation and by different methods staining, are important, but, I think, fully recognized by all who ve worked for any length of time with these parasites.

I agree with Prof. Stiles in what he says regarding the transmission entamoeba by water. I do not believe that these parasites are thus ansmitted to any great extent. I see no theoretical objection to r. Stiles's theory of the transmission of the spores and cysts by the y, but I do not think that this insect is responsible in the Philippine slands, for the fly is a rare insect there, as everyone knows who has raveled through the country. I am inclined to believe that contact nfection and dust infection are greater sources of the disease than y transmission, at least in the Philippines.

Dr. SAMUEL T. DARLING: It is possible that my observations on he morphology of *E. tetragena*, and the observations recorded by Dr. Craig on the developmental phase of *E. histolytica*, in which pore formation by budding is described may be harmonized. The nonencysted forms of *E. tetragena*, showing four nuclei and division of the nucleus into four daughter nuclei, as Dr. Craig has suggested to me, may be identical with the forms noted by Dr. Craig in *E. histolytica*, i. e., the nuclei in the four nucleated naked forms may become pinched off to form new individuals. Unfortunately, at this time no observations tending to confirm this view have been made. There is something very characteristic about the pathological features of infection by *E. tetragena*, and I believe that, if there is more than one pathogenic entamoeba, we should expect to find more than one type of lesion. This does not seem to be the case, for the lesions caused by *E. tetragena* are unique and unvarying, and they are exactly like the lesions described elsewhere in the tropics as being caused by *E. histolytica*. In my opinion, the pathogenic entamoeba is one having the essential characteristics of *E. tetragena* with four nucleated cysts.

The statement by Dr. Stiles that *E. coli* disappears from the stools after the administration of flowers of sulphur interests me a great deal. As some of you may know, the mode of treatment for entamoebic dysentery at Ancon Hospital is the administration of large doses of bismuth. Stools from cases treated in this way by means of bismuth contain from 10 to 12 per cent by weight of bismuth subnitrate. The stools are frequently quite black, and, upon microscopic examination, I found the color to be due partly to a deposit of black bismuth sulphide on the surfaces of the white bismuth subnitrate crystals, and in part to the staining of micrococci and bacteria, for they had assimilated the bismuth salts into their substance, and

this had become changed into black bismuth sulphide. The stu
were usually free from fetid odor and from odors suggestive o
hydrogen sulphide. At the same time, I confirmed the observa
that trophozoites of *E. tetragena* usually disappear from fae
within two or three days after the administration of large dose
bismuth subnitrate. It would thus appear that while, according
Dr. Stiles's observations, *E. coli* is removed by administration
sulphur, *E. tetragena* disappears coincidently with the abstract
and locking up of sulphur in the bacteria and intestinal conten
the bismuth subnitrate.

THURSDAY AFTERNOON, SEPTEMBER 26, 1912.

LIST OF PARASITIC AMŒBÆ, ARRANGED ALPHABETICALLY.

HOWARD CRAWLEY, Assist. Zoologist, United States Department of Agriculture, Washington, D. C.

The following list, which is believed to contain all the names which ave been applied to parasitic amœbæ, is arranged alphabetically so ar as the specific names are concerned. Under each species name is laced the one or more generic names with which the species name as been combined. With one exception, these combinations refer o the same organism; thus, *histolytica* has been combined with five ifferent generic names, but each one of these five combinations re- ers to the same organism. The exception is the species *intestinalis*. Valker uses the name *Ameba intestinalis* (which Doflein puts into he genus *Entamœba*), but states it is not the same form as that amed *Amœba intestinalis* by Blanchard.

It has not been considered advisable to attempt a determination f the status of these various forms according to the International Code.

The titles and places of publication of the references given will be found in the paper by Dr. Albert Hassall, entitled "Bibliography of parasitic amœbæ."

africana

Amoeba Brumpt, 1910, p. 32.

Entamoeba Hartmann in Hartmann & Prowazek, 1907, p. 312 footnote.

apis

Entamoeba Fantham & Porter, 1911, p. 626.

arborescens

Amoeba Celli & Fiocca, 1894 b, p. 439.

aulastomi

Entamoeba Nöller, 1912, p. 195.

blattae

Amoeba Bütschli, 1878 a, pp. 273–277.

Endamoeba Leidy, 1879 a, p. 300; 1879 k, p. 205.

Entamoeba Doflein, 1909, p. 499.

blattarum

Amoeba Calandruccio, 1890 a, p. 99.

Entamoeba Casagrandi & Barbagallo, 1897. p. 163.

blochmanni
Amoeba Doflein, 1901 a, pp. 17–18.
bovis
Amoeba Liebetanz, 1905 a, p. 314.
Entamoeba Doflein, 1909, p. 499.
brasiliensis
Loeschia Chatton, 1912, p. 182.
? de Beaurepaire Aragão, 1912.
buccalis
Amoeba Steinberg, 1862 a.
Entamoeba Prowazek, 1904, p. 42.
buetschlii
Entamoeba Prowazek, 1912, p. 245.
chaetognathi
Amoeba Grassi, 1882 a, pp. 185–187.
chironomi
Amoeba Porter, 1909, pp. 32–41.
ciliaris
Amoeba Graham, 1899 a, p. 477 (*ciliata*, p. 515, *ciliaris* renamed).
cobayae
Ameba Walker, 1908, pp. 429, 442 (spelled *copayae*, p. 429).
cochinchinensis
Entamoeba Sluiter & Swellengrebel, 1912, pp. 23, 24.
coli
Amoeba Loesch, 1875 a, p. 210.
Endamoeba Schubotz, 1905 b, p. 34.
Entamoeba Schaudinn, 1903 a, p. 564.
Loeschia Chatton, 1912, p. 181.
coli communis
Amoeba Kruse, 1896 a, p. 613.
coli dysenteriae
Amoeba Doflein & von Prowazek, 1908, p. 918.
coli dysenterica
Amoeba Jansen, 1898 a, p. 134.
coli dysenterici
Amoeba Kruse, 1896 a, p. 613.
coli felis
Amoeba Quincke & Roos, 1893 a, p. 1093.
coli hominis
Amoeba Kuenen, 1909, p. 564.
coli incapsulata
Amoeba Maggiora, 1891, p. 725.
coli intestini vulgaris
Amoeba Fenoglio, 1904, p. 252.
coli mitis
Amoeba Quincke & Roos, 1893 a, p. 1093.
coli nipponica
Entamoeba Walker, 1911, p. 279.
coli vulgaris
Amoeba Ziegler, 1895 a, p. 717.
croupogena
Amoeba Rivolta & Delprato, 1881 a.
crupogena
Ameba Perroncito, 1882 a, p. 95.

currens
Amoeba Metcalf, 1910, pp. 308–310.
dentalis
Amoeba Braun, 1883 a, p. 11.
Entamoeba Frosch, 1909, p. 191.
diaphana
Amoeba Celli & Fiocca, 1894 b, p. 438.
dissenterica
Amoeba Fenoglio, 1904, p. 251.
dysenteriae
Amoeba Councilman & Lafleur, 1891 a, p. 405.
Entamoeba Craig, 1905, pp. 245–289.
dysenterica
Amoeba Pfeiffer, 1888 c, p. 662.
Entamoeba Thornburgh, 1908 a, pp. 55, 56.
enterica
Ameba Walker, 1908 a, pp. 429, 443.
febris flavae
Amoeba Thayer, A. E., 1907 a, p. 49.
febris tertianae
Amoeba Kruse, 1896 a, p. 673 (name credited to Golgi).
fecalis
Ameba Walker, 1908 a, pp. 386, 429.
felis
Amoeba Quincke & Roos, 1893 a, p. 1093.
foliata
Amoeba Casagrandi & Barbagallo, 1897 a, p. 586. [No evidence that this is a parasite.]
gallopavonis
Ameba Walker, 1908 a, pp. 429, 444 (spelled *galloparvonis* on p. 429).
gengivalis
Amoebea Gros, 1849 a, p. 555.
gingivalis
Amoeba Braun, 1895 b, p. 44.
Entamoeba Castellani & Chalmers, 1910, p. 214.
guttula
Amoeba Celli & Fiocca, 1894 b, p. 436.
hartmanni
Entamoeba von Prowazek, 1912, p. 243.
histoltica
Amoeba Castellani, 1904, p. 509.
Entamoeba Castellani, 1904, p. 507.
histolitica
Amoeba Motas, 1906, p. 682 (error for *histolytica*).
histolytica
Amoeba Broido, 1903, pp. 827, 828.
Endamoeba Hickson, 1909, pp. 82, 83.
Entamoeba Schaudinn, 1903 a, pp. 564, 570.
Loeschia Chatton & Lalung-Bonnaire, 1912, pl. 9, facing p. 138.
Poneramoeba Luehe, 1909, p. 421.
histolytica dysenteriae
entamoeba Hara, 1910, pp. 340, 367.
histolytica tetragina
Entamoeba Walker, 1911, p. 279.

hominis
Amœba Walker, 1908 a, pp. 429, 444.
Entamœba Casagrandi & Barbagallo, 1897, p. 168.
Paramœba Craig, 1906, p. 214.
hystolitica
Endamœba Schubotz, 1905 b, p. 34.
hystolytica
Amœba Jelks, 1910, p. 55.
incapsulata
Amœba Wesener, 1892 a, p. 541.
intestinalis
Amœba R. Blanchard, 1885 g, p. 15.
intestinalis
Amœba Walker, 1908 a, pp. 414, 429.
Entamœba Doflein, 1909, p. 506.
intestinalis vulgaris
Amœba Eichhorst, 1901 a, p. 292.
intestini vulgaris
Amœba Quincke & Roos, 1893 a, p. 1093.
istolitica
Amœba Fenoglio, 1904, pp. 251, 252.
iurai
Endamœba Hickson, 1909, p. 83 (error for *miurai*).
jelaginia
Amœba von Mereschowsky, 1878 a, p. 204.
kartulisi
Amœba Doflein, 1901 a, p. 30.
Entamœba Doflein, 1909, p. 506.
lacertae
Amœba Hartmann in Hartmann & von Prowazek, 1907, p. 314.
Vahlkampfia Chatton, 1912, p. 112.
lagopodis
Amœba (*Entamœba*) Fantham, 1910, p. 702.
letullei
Amœba Letulle, 1908, pp. 256–266.
limax
Amœba Pfeiffer, 1891 a, p. 211.
lobosa
Amœba Celli & Fiocca, 1894 b, p. 436.
lobosa coli
Amœba Celli & Fiocca, 1894, b, p. 436.
lobosa gruberi
Amœba Wuelker, 1911, p. 592.
lobosa guttula
Amœba Celli & Fiocca, 1894 b, p. 436.
lobosa oblonga
Amœba Celli & Fiocca, 1894 b, p. 436 (name credited to Schmarda).
lobospinosa
Amœba Craig, 1912, pp. 1, 25–30.
loeschi
Entamœba Lesage, 1908, p. 105.
malariae (hominis)
Amœba Sakharov, 1892 a.

malariae febris quartanae
Amœba Kruse, 1896 a, p. 672 (name credited to Golgi).
maxillaris
Entamœba Kartulis, 1906, p. 356.
meleagridis
Amœba Smith, 1895 a, pp. 1–88.
Entamœba Doflein, 1909, p. 508.
melegridis
Amœba Cole, 1906, p. 297.
meliagridis
Amœba Walker, 1908 a, p. 446 (error for *meleagridis*).
minuta
Amœba Gedoelst, 1911, p. 88.
Entamœba Elmassian, 1909, p. 335.
Loeschia Chatton, 1912, p. 182.
mitis
Amœba Cramer, 1896 a, p. 148.
murai
Amœba Ijima, 1898 a, p. 85.
Endamœba Hickson, 1909, p. 88 (spelled *turai*, obviously a misprint).
Entamœba Castellani & Chalmers, 1910, p. 214.
mortinatalium
Amœba Gedoelst, 1911, p. 88.
Entamœba Smith & Weidman, 1910, pp. 285–298.
morula
Entamœba Raff, 1912, pp. 346–351.
muciçola
Amœba Chatton, 1909, p. 690.
muris
Amœba Grassi, 1882 a, pp. 181–182.
Entamœba Hartmann, 1907, p. 148.
Proctamœba Alexeieff, 1912, p. 64.
musculi
Ameba Walker, 1908 a, pp. 429, 447.
nipponensis
Entamœba Doflein, 1911, p. 579.
nipponica
Amœba Gedoelst, 1911, p. 88.
Entamœba Koidzumi, 1909, p. 650.
nuttali
Entamœba Castellani, 1908, p. 102.
oblonga
Amœba Celli & Fiocca, 1894 b, p. 436 (name credited to Schmarda).
ondulans
Entamœba Billet, 1907, p. 217 (error for *undulans*).
paedophthora (variously spelled).
Amœba Caullery, 1906, p. 267.
Entamœba Castellani & Chalmers, 1910, p. 215.
Vahlkampfia Chatton, 1912, p. 112.
parasitica
Amœba Lendenfeld, 1885 a, pp. 35–88.
phagocytoides
Amœba Gedoelst, 1911, p. 82.
Entamœba Gauducheau, 1907, pp. 486–487.

pigmentifera
Amoeba Grassi, 1881, p. 354.
pitheci
Entamoeba von Prowazek, 1912, p. 246.
polecki
Entamoeba von Prowazek, 1912, p. 274.
pulmonalis
Amoeba Artault, 1898, pp. 275–277.
Entamoeba Castellani & Chalmers, 1910, p. 214.
ranae
Ameba Walker, 1908 a, pp. 429, 447.
Entamoeba Hartmann, 1907, p. 143.
ranarum
Amoeba Grassi, 1879 m, p. 446.
Entamoeba Dobell, 1908, p. 428.
Proctamoeba Alexeieff, 1912, p. 66.
ranorum
Entamoeba Castellani & Chalmers, 1910, p. 215 (error for *ranarum*).
reticularis
Amoeba Celli & Fiocca, 1894 b, p. 439.
rotatoria
Amoeba Mayer, 1843 a, p. 11.
sagittae
Amoeba Grassi, 1881, p. 354.
salpae
Proctamoeba Alexeieff, 1912, p. 64.
schaudinni
Entamoeba Lesage, 1908, p. 105.
spinosa
Amoeba Celli & Fiocca, 1894 b, p. 437.
succinea
Amoeba Pfeiffer, L., 1891 a, p. 211.
testudinis
Entamoeba Hartmann, 1909, p. 209.
tetragena
Amoeba Hartmann, 1908, p. 126.
Entamoeba Viereck, 1907 c, p. 82.
Loeschia Chatton & Lalung-Bonnaire, 1912, pl. 9 facing p. 138.
Viereckia (subgenus) Chatton & Lalung-Bonnaire, 1912, p. 142.
tetragina
Entamoeba Walker, 1911, p. 276.
tetragona
Entamoeba Hartmann in Hartmann & von Prowazek, 1907, p. 312 footnote (error for *tetragena*).
tropicalis
Amoeba Gedoelst, 1911, p. 33.
Entamoeba Lesage, 1908, p. 105.
undulans
Amoeba Celli & Fiocca, 1894 b, p. 436 (as variety of *Amoeba lobosa*; not specifically stated to be a parasite).
undulans
Endamoeba Hickson, 1909, p. 33.
Entamoeba Castellani, 1904, p. 508.

enitalis
Ameba Walker, 1908 a, p. 423 (eror for *urogenitalis*).
genitalis
Amoeba Baelz, 1883 a, p. 237.
Entamoeba Doflein, 1909, p. 505.
inalis
Amoeba R. Blanchard, 1885 g, p. 15.
micularis
Amoeba Celli & Fiocca, 1894 b, p. 438 (credited to Weisse).
idis
Amoeba Wuelker, 1911, p. 609.
garis
Amoeba Roos, 1894 c, p. 391.
liamsi
Entamoeba von Prowazek, 1911, p. 349.
laginia
Amoeba Broïdo, 1903, p. 33 (error for *jelaginia*).

The several genera named above, with their type species, are given the following list:

moeba proteus.
ndamoeba blattae Leidy, 1879 a, p. 300; 1879 k, p. 205.
ntamoeba histolytica Schaudinn, 1903 a, pp. 564, 570.
oeschia coli Chatton, 1912, p. 110.
ramoeba eilhardi Schaudinn, 1896 b, p. 31.
oneramoeba histolytica Luehe, 1909, p. 421.
roctamoeba synonym of *Loeschia.*
'ahlkampfia vahlkampfi Chatton, 1912, p. 112.

DER KERNAUFBAU DER PARASITISCHEN AMÖBEN.

Dr. M. J. S. von Prowazek, Seemannskrankenhaus und Institut für Schiffs- und Tropenkrankheiten, Hamburg, Germany.

Bei einer Besprechung des Kernaufbaues der parasitischen Amöben ist es zunächst notwendig, den innerhalb ziemlich weiter Grenzen schwankenden Begriff des Parasitismus dieser Amoeben irgendwie abzugrenzen.—Für eine derartige Begriffsabgrenzung ist in erster Linie eine genaue Kenntnis der gesamten biologie der fraglichen Organismen, die leider bis jetzt bie den Amöben nur sehr lückenhaft bekannt ist, vorbedingung. Aus diesem letzteren Grunde müssen wir eine künstliche Abgrenzung der parasitischen Amöben vornehmen, und wir ziehen in den Rahmen unserer Betrachtung nur solche Formen ein, deren Weiterentwicklung notwendig an einen Wirt gebunden ist und die daher ausserhalf eines Wirtstieres auf längere Zeit in der freien Aussenwelt nicht leben können und aus diesem Grunde vermutlich nicht oder schwer züchtbar sind. Auf Grund dieser Annahme scheiden aus unserer Betrachung alle Amöben aus, die

gelegentlich in den Körperhöhlen eines Zwischenwirts vorkommen knönen—es sind dies alle Amöben des Limaxtypus, wie z. B. *Amoeba lacertae*, die Nägler selbst als einen Saprophyten aufgefasst hatte.

Bei unserer Untersuchung werden uns hauptsächlich Repräsentanten der Gattung *Entamoeba* beschäftigen; diese Formen sind bis jetzt gleichfalls nicht im strengen systematischen Sinne definierbar, da wir ihren ganzen Entwicklungszyklus nicht kennen und die Frage, ob bei allen eine Autogamie oder Heterogamie bezw. Paedogamie vorkommt, das Verhalten ihrer Chromidien u. a. m. definitiv noch nicht erledigt ist.

Von den parasitischen Amöben müssen wir ferner diejenigen Formen ausscheiden, bei denen der gesamte Kernaufbau noch nicht untersucht bezw. noch nicht beschrieben worden ist—denn Angaben, dass der Kern rund oder bläschenförmig ist und im Zentrum einen "Nucleolus" oder ein "Karyosom" enthält, genügen den Ansprüchen moderner Zytologie nicht mehr. Es sind dies folgende Amöben:

(1) *Amoeba bovis* Liebetanz (hab. *Bos taurus*).

(2) *Amoebo cobayae* n. sp. E. L. Walker "Nucleus circular in outline, but plastic surrounded by a hyaline halo, otherwise homogeneous."

(3) *Amoeba gallopavonis* n. sp. E. L. Walker (hab. *Meleagris gallopavo*).

(4) *Amoeba intestinalis* E. L. Walker (hab. *Equus caballus*, *Sus scorfa domestica*, *Felis domestica*, *Meleagris gallopavo*).

(5) *Amoeba kartulisi* Doflein (hab. *Homo sapiens*).

(6) *Amoeba urogenitalis* Baelz (hab. *Homo sapiens*).

(7) *Entamoeba phagocytoides* Gauducheau (hab. *Homo sapiens*).

(8) *Entamoeba undulans* Castellani (hab. *Homo sapiens*).

(9) *Entamoeba nutalli* Castellani (hab. *Macacus pillatus*).

Die Kernstruktur ist bei folgenden Amöben genauer, wenn auch nicht vollstädig bekannt geworden:

A. Entamöben mit typischem Karyosomkern:

(1) *Entamoeba coli* Schaudinn und ihre Varietät *Entamoeba williamsi* Prowazek (hab. *Homo sapiens*).

(2) *Entamoeba buccalis* Prowazek (hab. *Homo sapiens*).

(3) *Entamoeba histolytica* Schaudinn (hab. *Homo sapiens*).

(4) *Entamoeba tetragena* Viereck (hab. *Homo sapiens*).

[Falls die "Brutbildung," die Schaudinn bei *E. histolytica* beschrieben hatte, sich nicht bestätigen sollte und die Tetragenacysten tatsächlich in den Entwicklungskreis der Histolytica hineingehören, so muss der Name der *später* beschriebenen *Ent. tetragena* zu Gunsten der *Entamoeba histolytica* verschwinden. Ausser den Angaben Schaudinns wäre jedoch immer noch die zweite Mitteilung Craigs sowie Lesages für die Selbständigkeit der Histolytica anzuführen;

sserdem aber der von A. Kuenen und Werner betonte Umstand, ss es Amöbendysenterien gibt, bei denen Amöben ohne Tetragenasten mit Histolyticatypus vorkommen.]

(5) *Entamoeba minuta* Elmassian, von einigen Autoren als selbstindige Art angezweifelt (hab. *Homo sapiens*).

(6) *Entamoeba nipponica* Koidzumi (hab. *Homo sapiens*, vergl. ie 5).

(7) *Entamoeba hartmanni* n. sp. Prowazek (hab. *Homo sapiens*, üdsee).

(8) *Entamoeba pitheci* Prowazek (hab. *Orang-utan*).

(9) *Entamoeba polecki* Prowazek (hab. *Sus scorfa*, gelegentlich *lomo sapiens*).

(10) *Entamoeba muris* Grassi (hab. *Mus*).

((1) *Entamoeba testudinis* Hartmann (hab. *Testudo graeca*).

(12) *Entamoeba ranarum* Grassi (hab. *Rana esculenta*).

(13) *Entamoeba aulastomi* Nöller (hab. *Aulastomum gulo*).

B. Entamoeben mit einem Karyosomkern, in dem neben dem Karyosomkern noch Chromatinnukleolen (Janicki) vorkommen.

(14) *Entamoeba blattae* Bütschli.

C. Amöben, deren Parasitismus noch unklar ist:

(1) *Chlamydophrys-Leydenia gemmipara* (Schaudinn).

Der Kern der Leydenia ist rund, bläschenförmig, besitzt einen mit Boraxkarmin, Thionin, Brasilin färbbaren "Pseudonukleolus" und eine helle, chromatinfreie, wabig gebaute Kernsaftzone. Kerndurchmesser ca. 5 μ, Kernsaftzone ¾ μ, Kernteilung amitotisch, der Pseudonukleolus schnürt sich durch; Kernknospung wurde gleichfalls beschrieben (hab. *Homo sapiens*) in zwei Fällen von Carcinom v. Leyden beobachtet. Nach einer späteren Mitteilung Schaudinns gehört Leydenia zu Chlamydophrys.

(2) *Paramoeba hominis* (hab. *Homo sapiens*) Ch. F. Craig hat zuerst bei eigenartigen Diarrhoen in Manila eine Paramoeba beschrieben und ihre Entwicklungsgeschichte beobachtet. Eine Schilderung der feineren Kernstrukturen steht noch aus.

FORM DES KERNES.

Bei allen diesen Amöben ist der Kern mehr oder weniger sphaerisch rund oder rundlich; bei *Ent histolytica* verändert er nach Schaudinn und Hartmann gelegentlich wahrend des Lebens seine Gestalt und wird bei der Bewegung passiv leicht verzerrt, exzentrisch verlagert und zusammengepresst. Für den Kern der *Ent. blattae* nahm Schubotz and, dass er gelegentlich aktiv veränderlich werden kann. Janicki konnte sich von einer aktiven Beweglichkeit nicht überzeugen und erklärte mit Mercier die bereits von Bütschli gelegentlich beobachteten "geschnabelten" Kerne für Kernindividuen, die eben aus der Teilung hervorgegangen sind.

GRÖSSE DER KERNE.

Der Durchmesser der Kerne schwankt ausserordentlich. Junge Amöben von *Ent. aulastomi* besitzen Kerne, deren Durchmesser 7.5 μ beträgt, grosse, erwachsene Formen erreichen einen Kerndurchmesser von 10 μ. Bei *Ent. blattae* fand Schubotz den Durchmesser kugeliger Kerne 15–20 μ, die obere Grenze dürfte 30 μ nicht überschreiten. Der Kern von *Ent. testudinis* beträgt 12.5 oder 11.5 zu 15 μ. Der Kern von *Ent. ranarum* hat nach Dobell einen Durchmesser von 4.4 μ. Bei *Ent. hartmanni* kommen in ein und derselben Zyste neben grossen Kernen auch kleine Kerne vor.

KERNSTRUKTUREN.

(1) *Kernmembran.*

Alle Entamöben besitzen wahrscheinlich eine Kernmembran. Bei *Ent. coli*, *buccalis*, *tetragena*, *minuta*, *nipponica*, *hartmanni*, *pitheci* und *polecki* kommt eine gleichmässig ausgebildete Kernmembran vor, bei *Entamoeba testudinis* ist der Kern gegen das Plasma durch eine deutliche, doppelkonturierte, derbe Kernmembran abgegrenzt. Auffallend dick ist die Kernmembran bei *Ent. blattae* (1–2 μ) und Schubotz konnte in ihr zwei Strukturschichten unterscheiden; die innere Schicht soll dünner sein als die äussere. Von anderen Autoren werden die Angaben, die sich auf die Membrandicke von 1–2 μ beziehen, angezweifelt. Von dem Kern der *Ent. histolytica* schreibt Hartmann 1909: "Im Gegensatz zu *E. coli* (Schaudinn 1904) und *E. tetragena* (Hartmann 1908) besitzt der Kern keine doppelt konturierte achromatische Membran, die bei den beiden anderen Arten ziemlich derb ist."

Awerinzew (Archiv für Protistenkunde, 1906, S. 115) unterscheidet bei Süsswasserrhizopoden von einer protoplasmatischen Hülle des Kernes noch die eigentliche strukturlose Kernmembran, vielleicht ist die, protoplasmatische Hülle mit dem "feineren Saum von gleich grossen, stark lichtbrechenden Körnchen" zu vergleichen, die nach Werner (Handbuch der pathogenen Protozoen, S. 70) die Kernmembran der *Ent. coli* zuweilen umgeben.

Nöller konnte bei *Ent. aulastomi* eine Kernmembran nicht nachweisen.

(2) *Chromatin der Kernsaftzone-Aussenchromatin (Aussenkern).*

Der sogenannte Aussenkern der Entamöben stellt eine Hohlkugel dar, in der peripher gegen die Kernmembran über ein anscheinend meist wabiges Achromatin (Kerngerüst, Linin) Chromatin in Körnchenform von verschiedener Grösse und Mächtigkeit verteilt ist. Diese Verhältnisse sind bei *Ent. coli* von Schaudinn, Werner,

artmann und Prowazek, bei *Ent. tetragena* von Viereck, Werner, artmann u. a., bei *Ent. buccalis* von Prowazek, Löwenthal, bei *nt. williamsi*, *hartmanni*, *pithoci*, *polecki* von Prowazek, bei *Ent. ılastomi* von Nöller, bei *Ent. muris* sowie einer Amöbensp. aus der laus von Wenyon, bei *Ent. testudinis* von Hartmann u. a. m. im leichen Sinne beschrieben worden.

Von der *Ent. nipponica* schreibt Koidzumi: "The nuclear plasm oes not show either reticular or alveolar structure. The nucleus is ery rich in chromatin, which is found condensed into several clumps nd closely situated on the inner surface of the nuclear membrane."

Komplizierter ist der Kern der *Ent. blattae* gebaut; fassen wir die on einander etwas differierenden Beschreibungen des Kernaufbaues on Schubotz, Elmassian, Mercier und Janicki zusammen, so folgt uf die innere Schichte der Kernmembran eine wabig gebaute peri-here Kernzone (*a*) mit feinem Chromatin, die zentral einen hellen, örnchenfreien, wabigen Innenraum (*b*) einschliesst; an der Grenze wischen beiden liegen meist kugelig 2–5 μ grosse chromatische "Nu-leolen" (*c*). In dem Innenraum ist zuerst von Janicki ein meist in Vorbereitung zur Teilung befindliches Karyosom (Netrum nach Boveri) nachgewiesen worden (*d*).

Der Aussenkern der Entamöben ist von dem Karyosom vielfach durch eine helle Kernsaftzone getrennt.

(3) *Karyosom.*

Das Karyosom der Entamöben ist ein wichtiger und notwendiger Kernbestandteil, der morphologisch aus Chromatin und Plastin besteht, wobei das erstere Kernelement zunächst in Körnchenform reichlich in das Plastin eingetragen ist. Wie weit das Chromatin aus Plastin im Sinne von Moroff u. a. entstehen und umgekehrt sich wieder zurückverwandeln kann, ist nach dem derzeitigen Stande der mikroskopischen Technik Vent Sicherhert nachzuweisen nicht möglich. Nach Hartmann ist für die Existenz eines echten Karyosoms der Nachweis eines zentralen Centriols ("Centrosom") eine Notwendigkeit; fehlt ein Centriol, so muss man die sonst morphologisch gleichen Kerngebilde als Pseudokaryosome bezeichnen. Gläser (Archiv für Protistenkunde, 25. Bd., 1. Heft, 1912) vertritt insofern einen anderen Standpunkt, als nach ihm das allgemeine Vorhandensein von Centriolen im Caryosom aller Protozoen nicht nur nicht bewiesen, sondern unwahrscheinlich ist. Als Karyosom definiert er die "Binnenkörper, die bei der Teilung ganz oder zum Teil als Nucleolocentrosom wirken." Für die Bezeichnung des Karyosoms wäre also die genaue Kenntnis ihrer Rolle bei der Kernteilung Vorbedingung. Als Nukleolocentrosomen oder in einem gewissen Sinne als Netren (Boveri) teilen sich nun die Binnenkörper bei *Ent. buccalis* (Prowazek), *Ent. tetagena* (Hartmann) bei *Ent. Blattae* (Janicki), bei einer

Amöbensp. aus der Maus (Wenyon) vielleicht bei der *Ent.* [illegible] (Wenyon) und *Ent. ranarum* (Dobell), bei den übrigen Amöben scheint mir der Kernteilungsvorgang noch nicht in diesem Sinne genau untersucht worden zu sein und auch bei den oben genannten Amöben " verschwindet " auf manchen gerade entscheidenden Stadien der Spindelbildung das Karyosom als selbständiges Kerngebilde, als Nukleocentrosoma in der Gesamtspindel und man kann sich von seiner von der modernen Zytologie betonten Gesamtkontinuität nicht überzeugen. Bei *Ent. coli* und *tetragena* scheinen auf der Höhe der Spindelentwicklung der Aussenkern und Karyosomkern sich ganz durchzumischen und ihre Sonderung aufzugeben, zumal auch die Centriolen nicht immer nachweisbar sind.

Die unvollkommene Kenntnis der Kernteilung kann uns also zunächst keine Direktiven für die schwierige Terminologie der einzelnen Kernbestandteile liefern. Kehren wir zu der letzten Definition Hartmanns zurück, so ist ein Centriol bis jetzt sicher nur im Karyosom der *Ent. tetragena* (Hartmann), *Ent. coli* (Hartmann), *Ent. aulastomi* (Nöller) sowie *Ent. testudinis* (Hartmann) nachgewiesen worden; zeitweise beobachtet ist es bei *Ent. muris*, *Ent. buccalis*, *Ent. polecki* sowie *Ent. blattae*, bei der aber nach Janicki zuweilen sogar das ganze Karyosom verschwinden soll. Auch Dobell betont im Gegensatz zu Grassi (1881) das Fehlen eines Karyosoms bei *Ent. ranarum*. Gläser meint, dass bei allen Entamöben der kurz vor der Teilung gebildete Binnenkörper (Karyosom) überhaupt aufgelöst wird. Bei allen Formen, bei denen die Kontinuität eines Karyosoms durchbrochen ist, wird sich aber de facto eine Kontinuität eines kleinen Körnchens wie es das Centriol ist, kaum nachweisen lassen— sie bleibt nur ein theoretisches Desideratum.

Bei *Ent. minuta* konnte Elmassian im Karyosom kein Centriol nachweisen, bei den übrigen Amöben sind sonst auch keine Centriolen beschrieben worden.

Aus dieser Zusammenstellung geht hervor, dass sowohl die Definition des Karyosoms als des Centriols und die Lehre der Kontinuität leider noch strittig sind und dass nur eine weitere Forschung ohne theoretische Voreingenommenheit Klarheit in die verwickelte Sachlage bringen kann. Vorläufig scheint es aber zweckmässig zu sein, das zentrale Plastinchromatingebilde, das im Kern der Entamöben zumeist ausgebildet ist, als Karysom zu bezeichnen, ohne sich an den Nachweis der Centriolen, der praktisch nicht immer durchführbar ist, zu klammern.

ZYKLISCHE PROZESSE AM KARYOSOM.

Im Anschluss an die theoretisch wichtigen Untersuchungen über das Centrosom von Boveri sowie an die späteren Untersuchungen über den Blepharoplast und das Karyosom der Flagellaten (1904) wurden

ch am Karyosom periodisch einsetzende Abbauprozesse beobach-
. In dem in einer bestimmten Zeiteinheit fixierten mikrosko-
schen Bilde stellen sie sich als chromatische Wellen von verschie-
ner Mächtigkeit und variablem Radius dar, die von einem
regungszentrum (Karyosom-Centriol) ausgehen und membran-
irts fortschreiten. Zyklische Vorgänge sind besonders bei *Ent.*
tragena und *testudinis* von Hartmann beobachtet worden, zeit-
eise kommen sie auch bei *Ent. coli* (Werner) vor, ferner sind sie
i *Ent. polecki* geschildert worden. Auch bezüglich dieser zy-
ischen Prozesse ist die Auffassung der verschiedenen Autoren nicht
nheitlich, so schreibt H. Gläser (1912) "Es ist zum mindesten ver-
früht, im Auf- und Abbau des Karyosoms zyklische Vorgänge zu
hen, wie sie den Centrosomen der Metazoen eigen sind. Sicher
t nur, dass bei den Entamöben der kurz vor der Teilung gebildete
innenkörper wieder aufgelöst wird."

BEDEUTUNG DES KARYOSOMS FÜR DIE DIAGNOSE.

Bis jetzt ist es ungemein schwer, die einzelnen vegetativen Stadien
er Entamöben von einander zu unterscheiden—da man aber zumeist
ur vegetative Stadien findet, wäre eine solche Unterscheidung auch
ür die Praxis wichtig, die sich immer wieder mit der Frage, ob
Ent. coli, *histolytica* oder *tetragena* vorliegt, beschäftigen muss.
Im Anschluss an die Untersuchungen von Schaudinn hat Hartmann
owie F. Craig das Karyosom und seine Struktur der Entamöben bei
er Differentialdiagnose der Formen berücksichtigt.

Nach Hartmann, Whitmore, und Craig ist das Karyosom der *Ent.*
coli ähnlich dem der *Ent. tetragena*, die in ihrem Kernaufbau in
die Mitte zwischen *Ent. histolytica* und *tetragena* zu stellen ist, nur
spielen sich im Gegensatz zu den Angaben von Werner nicht so
typische zyklische Prozesse an ihm ab, ferner ist bie *Ent. coli* in
20–30 Prozent von allen Individuen das Karyosom immer in Tei-
lung begriffen. Bei *Entamoeba histolytica* ist ein kleines Karyosom
vorhanden (Schaudinn, Hartmann, Craig), das Aussenchromatin
ordnet sich oft in Klumpen- oder Pigmentform peripher an, die
doppelt konturierte Kernmembran fehlt und der Kern liegt meist
excentrisch. Der grosse Wert dieser Diagnose ist aber von verschie-
denen Autoren angezweifelt worden, so teilweise von H. Werner,
A. Kuenen u. a. m.

KERNTEILUNG.

Ueber das Wesen der Kernteilung der Entamöben können wir uns
zur Zeit keine abschliessende Vorstellung bilden, da bei keiner Amöbe
alle Stadien beobachtet worden sind. Einzelne Kernteilungsbilder

COMPENDIUM OF ALL AMEBAE, ARRANGED ACCORDING TO THE HOSTS, REGARDLESS OF THE ZOOLOGICAL STATUS OF THE SPECIES OF AMEBAE.

By ALBERT HASSALL, Assistant Zoologist, United States Department of Agriculture, Washington, D. C.

APIS MELLIFICA:
apis Fantham & Porter: Entamoeba.
AULASTOMUM GULO:
aulastomi Noeller: Entamoeba.
BEE. See *Apis mellifica.*
BLATTA ORIENTALIS:
blattae Buetschli: Amoeba, Endamoeba.
blattarum Calandruccio: Amoeba.
sp.: Amoeba.
BOMBINATOR PACHYPUS:
currens Metcalf: Amoeba (Entamoeba).
BOS TAURUS:
bovis Liebetanz: Amoeba.
coli Loesch: Amoeba.
oblonga Celli & Fiocca: Amoeba.
BOX BOOPS:
sp. Chatton: Amoeba.
BUFO CINEREUS:
currens Metcalf: Amoeba (Entamoeba).
BUFO VULGARIS:
ranarum (Grassi): Entamoeba.
CANIS FAMILIARIS:
coli Loesch: Amoeba, Endamoeba, Entamoeba
fecalis Walker: Ameba.
phagocytoides Gauducheau: Entamoeba.
CAT. See *Felis domestica.*
CAVIA COBAYA:
cobayae Walker: Ameba.
coli Loesch: Amoeba.
fecalis Walker: Ameba.
spinosa Celli & Fiocca: Amoeba.
CHIRONOMUS SP. (larva):
chironomi Porter: Amoeba.
COLUMBA DOMESTICA:
croupogena Rivolta & Delprato: Ameba.
DOG. See *Canis familiaris.*
EIDECHSE. See *Lacerta.*
EQUUS CABALLUS:
coli Loesch: Amoeba.
fecalis Walker: Ameba.
intestinalis Walker: Ameba.
letullei Neveu-Lemaire: Amoeba.
FELIS DOMESTICA:
coli Loesch: Amoeba.
coli felis Quincke & Roos: Amoeba.
coli mitis Quincke & Roos: Amoeba.

mmen nich nur aus dem Kern, sondern nehmen im Plasma an Grösse d Zahl enorm zu." Im Laufe der Enzystierung klumpen sie sich zu iem Chromidalkörper zusammen. Ihre Bedeutung ist nicht voll- mmen klar, "wahrscheinlich handelt es sich um einen Reserve- ff, denn im weiteren Verlauf der Cystenbildung un der sich schliessenden Cystenruhe werden diese Körper in der Regal ganz er fast ganz aufgebraucht." Ueber Chromidien der *Ent. coli* gen Beobachtungen von Schaudinn, Werner, und Hartmann vor; ie bei *Ent. williamsi* werden die Chromidien in noch jungen ysten unter Strömungserscheinungen nach aussen abgestossen oder rerklumpen zu einem grossen Chromidialkörper, der in der Cyste degeneriert." Bei *Ent. williamsi*, bei der die Chromidien oft wetz- einförmig und fast kristallinisch aussehzen, liegen sie später oft appenförmig der fertigen Cyste an. Werner lässt bei *Ent. coli* auch om peripheren Kernchromatin Chromidien entstehen. Bei *Ent. artmanni* kommt in der Cyste ein bakteroides, stäbchenförmig estaltetes Chromidium in Ein- bis Zweizahl vor. Bei *Ent. histoly- ica* rückt nach Schaudinn-Hartmann das Karyosom an die Kernmem- ran heran und gibt chromatisches Material an das Plasma ab, später rfahren die Chromidialbrocken selbsttätig eine Vermehrung, worauf er Kern zusammenschrumpft "entweder ganz aufgelöst oder aus er Zelle eliminiert" wird. Auf diese Weise entstehen die sog. hromidialtiere (Hartmann) (vergl. *Ent. buccalis*); ähnlich wie chaudinn liefert Craig (1908) eine Schilderung der Chromidien- ystenbildung der *Ent. histolytica* (vergl. noc. 1909). Chromidien at ferner W. Nöller bei *Ent. aulastromi* beschrieben.

DEGENERATION DER KERNE.

Von fast allen Autoren, die sich mit der Untersuchung der Biologie der Entamöben beschäftigt haben, sind Kerndegenerationen beschrieben worden, die einen sehr mannigfachen Verlauf nehmen können, bezüglich der Einzelheiten muss auf die speziellen Arbeiten verwiessen werden. Die Kerndegeneration der *Ent. ranarum* hat Dobell zum Gegenstand einer besonderen Studie gemacht und sie mit der Depressionslehre Hertwigs in Zusammenhang gebracht. Bei *Ent. tetragena* unterscheidet Hartmann zwei Haupttypen von Degenerationsformen (*a*) Formen, bei denen sich das Chromatin in Form von grösseren Brocken an der Kernmembran ansammelt, (*b*) Formenreihen, bei denen die Kernmembran schwindet und nur noch ein grosses Karyosom übrig bleibt.

Ueber Kerndegenerationen bei *Ent. williamsi* hat Prowazek, bei *Ent. aulastomi* W. Nöller berichtet, ferner sind diesbezügliche Angaben in den Arbeiten von Casagrandi-Barbagallo sowie Noc zu finden.

HOMO SAPIENS—Continued.
polecki von Prowazek: Entamoeba.
pulmonalis Artault: Amoeba.
reticularis Celli & Fiocca: Ameba.
sp. Fantham: Entamoeba.
spinosa Celli & Fiocca: Ameba.
tetragena Viereck: Amoeba, Entamoeba.
tropicalis Lesage: Amoeba, Entamoeba.
undulans Celli & Fiocca: Amoeba.
undulans Castellani: Entamoeba.
urogenitalis Baelz: Ameba.
vaginalis Blanchard: Amoeba.
vermicularis Celli & Fiocca: Ameba.
viridis Wuelker: Amoeba.
vulgaris Roos: Amoeba.
williamsi von Prowazek: Entamoeba.
HORSE. See *Equus caballus*.
HOUSE MOUSE. See *Mus musculus*.
LACERTA:
lacertae Hartmann: Amoeba.
LACERTA AGILIS:
lacertae Hartmann: Amoeba.
LAGOPUS SCOTICUS:
lagopodis Fantham: Amoeba (Entamoeba).
sp. Shipley: Amoeba.
LEPUS CUNICULUS. [*See also* Rabbit.]
enterica Walker: Amoeba.
LIMAX:
limax Pfeiffer: Amoeba.
LYMNODYNASTES TASMANIENSIS:
morula Raff: Entamoeba.
MACACUS CYNOMOLGUS:
sp. Musgrave & Clegg: Amoeba.
MACACUS PHILIPPINENSIS:
sp. Musgrave & Clegg: Amoeba.
MACACUS PILEATUS:
nuttalli Castellani: Entamoeba.
MACACUS SINICUS:
sp. Chatton: Loeschia.
MELEAGRIS GALLOPAVO:
enterica Walker: Ameba.
gallopavonis Walker: Ameba.
intestinalis Walker: Ameba.
meleagridis Smith: Amoeba.
MOLGE PALMATA:
ranarum (Grassi): Entamoeba.
MONKEY:
lobospinosa Craig: Ameba.
sp. Fantham: Entamoeba.
tetragena Viereck: Entamoeba.
MUS DECUMANUS:
enterica Walker: Ameba.
spinosa Celli & Fiocca: Amoeba.

MUSCULUS:
enterica Walker: Ameba.
fecalis Walker: Ameba.
muris Grassi: Amoeba, Entamoeba.
musculi Walker: Ameba.
S RATTUS:
muris Grassi: Amoeba.
"Amibes" Stiles & Hassall.
'S spp.:
muris Grassi: Amoeba.
CORIA TRIJUGA:
testudinis Hartmann: Entamoeba.
IS ARIES:
parasitica Lendenfeld: Amoeba.
sp. Blanc: Amoeba.
ELTOGASTER CURVATUS:
paedophthora Caullery: Amoeba.
ERIPLANETA ORIENTALIS:
blattae Buetschli: Amoeba, Entamoeba.
IG. See *Sus scrofa.*
IGEON. See *Columba domestica.*
ITHECUS SATYRUS:
pitheci von Prowazek: Entamoeba.
LABBIT. [See also *Lepus cuniculus.*]
fecalis Walker: Ameba.
RANA ESCULENTA:
currens Metcalf: Amoeba (Entamoeba).
ranarum Grassi: Amoeba, Entamoeba.
spinosa Celli & Fiocca: Amoeba.
RANA sp.:
ranae Walker: Ameba.
rotatoria Mayer: Amoeba.
RANA TEMPORARIA:
ranarum (Grassi): Entamoeba.
RAT. See *Mus decumanus.*
RED GROUSE. See *Lagopus scoticus.*
SAGITTA CLAPARÈDEI:
chaetognathi Grassi: Amoeba.
pigmentifera Grassi: Amoeba.
sagittae Grassi: Amoeba.
SHEEP. See *Ovis aries.*
SPADELLA BIPUNCTATA:
chaetognathi Grassi: Amoeba.
pigmentifera Grassi: Amoeba.
sagittae Grassi: Amoeba.
SPADELLA INFLATA:
chaetognathi Grassi: Amoeba.
pigmentifera Grassi: Amoeba.
sagittae Grassi: Amoeba.
SPADELLA SERRATODENTATA:
chaetognathi Grassi: Amoeba.
pigmentifera Grassi: Amoeba.
sagittae Grassi: Amoeba.

HOMO SAPIENS—Continued.
polecki von Prowazek: Entamoeba.
pulmonalis Artault: Amoeba.
reticularis Celli & Fiocca: Ameba.
sp. Fantham: Entamoeba.
spinosa Celli & Fiocca: Ameba.
tetragena Viereck: Amoeba, Entamoeba.
tropicalis Lesage: Amoeba, Entamoeba.
undulans Celli & Fiocca: Amoeba.
undulans Castellani: Entamoeba.
urogenitalis Baelz: Ameba.
vaginalis Blanchard: Amoeba.
vermicularis Celli & Fiocca: Ameba.
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intestinalis Walker: Ameba.
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sp. Fantham: Entamoeba.
tetragena Viereck: Entamoeba.
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histolytica var. *tetragina* Walker, 1911, 279, pl. 5, fig. 13.

hominis Casagrandi & Barbagallo, 1897, 163.—Abu, 1905, 435.—Barbagallo, 1905, 73–75; 1905, 282; 1905, 145, 146; 1906, 380, 381.—Castellani & Chalmers, 1910, 220.—Fantham, 1911, 113, 116, 118.—Guiart, 1910, 142.—Kuenen, 1909, 549, 550, 551, 564.—Pruès, 1905, 30.—Schaudinn, 1903 a, 564.—Stiles, 1905 e, 296.—Verdun, 1904 f, 388; 1907 a, 29.—Viereck, 1907 c, 29.—Walker, 1908 a, 432, 440, 449.—Werner, 1911, 67.

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Viereckia Chatton & Lalung-Bonnaire, 1912, 142.
tetragena (Viereck, 1907).—Chatton, 1912, 110.

GENERA AND SPECIES OF AMOEBA.

By Dr. Gary N. Calkins, Professor of Protozoology, Columbia University, New York City.

"Die Kenntniss der Entwickelung ist das erste Postulat der Protozoenforschung. Schaudinn 1903."

The above quotation should be made an axiom and incorporated in every taxonomic paper on protozoa, especially on rhizopods. Until the full life history is known we can only place forms provisionally and with the understanding that further research alone will establish finality.

The taxonomic problems of the amoebae were not particulary difficult to handle until the pathogenic forms became known and artificial culture methods were developed. Then the difficulties were to determine between pathogenic and inocuous forms. Free living small amoebae may be cultivated with ease on artificial culture media, pathogenic forms less easily, and the problem of distinguishing between them soon began to give trouble. It is claimed by many that small forms of free living rhizopods may become encysted, and within the protection of their cysts withstand the digestive fluids of their vertebrate hosts, with or without emerging from their coverings. This led, furthermore, to the claim that all or a large proportion of the cultivated amoebae, said to be pathogenic or parasitic, were in reality only encysted stages of free living rhizopods. Within the last few years, therefore, there has been developed a great interest in the systematic positions of amoebae that will live on artificial culture media. The chief source of the confusion that has arisen is the group of minute water or infusion amoebae and not the relatively large free living forms like *Amoeba proteus*, *A. vespertilio*, and their allies. Some of the smaller ones are sufficiently characteristic to be easily identified. *A. verrucosa*, for example, with its corrugated surface, is not easily mistaken for other forms. It is different, however, with that group of minute forms usually included under the specific name *Amoeba limax* Dujardin.

At the present time it is recognized that the nature of the pseudopodia and ectoplasmic and endoplasmic differentiation are unsafe diagnostic characters by which to identify amoebae, for these have been shown to vary widely in the same species under different conditions of environment. Nuclear differences, however, appear to be more stable, and we find a growing tendency, mainly emphasized by Nägler, Chatton, and Gläser, to base specific differences on the changes which the nuclei undergo during division.

The enormous differences between amoeboid types of rhizopods not only justifies but makes imperative generic separation amongst them. The characteristics of *A. proteus* are definite and distinct, but the

characterization of a genus of which *A. proteus* is the type species would hardly suffice to characterize the widely divergent types that have been discovered in recent years. This conclusion has been independently reached by all students of the rhizopods, some of the results being seen in the genera Paramoeba and Entamoeba now well established.

The life history of *Amoeba proteus*, as well as the morphological features, is sufficient to separate it from the other and smaller free living forms that lend themselves to the agar culture method. The latter, belonging for the most part to the so-called "limax" group, have been extremely difficult to deal with systematically. Dujardin in 1841 created the species as a type of amoeba, but his description was so indefinite that no one at the present time can be sure of the form meant by this gifted pioneer. Penard in 1902 likewise gave an inadequate description, and many modern investigators, working with forms which they call *Amoeba limax*, have come to opposite conclusions regarding structures and activities, and much confusion has resulted. Vahlkampf in 1904 gave a careful description of a small form measuring about 3μ which he designated *A. limax*. The various phases of activity, including encystment, emergence from the cyst, and the details of nuclear division, were carefully made out. If we were to retain the name "limax," therefore, it would have to be based upon the characters described by Vahlkampf.

While retaining the specific name limax of Dujardin for Vahlkampf's species we agree with Chatton 1912 in giving it a different generic name from that of *Amoeba proteus* and accept Chatton's term Vahlkampfia as a generic name for part of the forms included formerly under the name Amoeba. We do not agree with Chatton, however, in abandoning the old name limax, but would retain it for the species *Vahlkampfia limax* Duj. emend Vahlk. Not only are forms included under the new genus Vahlkampfia different from *Amoeba proteus* but they also differ from other types of minute amoebae formerly included as limax forms. Here, for example, are those species which, on agar, pass from a pseudopodia bearing stage to a flagellum bearing stage, and vice versa. For these we have adopted Alexeieff's name Nägleria, but with emendations, however, since Alexeieff included under this name all of the forms herein grouped under the name Vahlkampfia.

The views expressed in the preceding paragraphs may be summarized in the statement that the old genus Amoeba should be broken up into allied genera as follows: Amoeba, Vahlkampfia, Nägleria, Craigia, Trimastigamoeba, Entamoeba, and Paramoeba.

NOTE.—No attempt has been made to make the bibliographies complete; the number of titles that might be added is legion, and no doubt many able works on the amoebae have been omitted. These can be obtained from the references cited.

GENERAL WORKS ON AMOEBAE.

Behla, R. 1897. Die Amöben, insbesondere vom parasitären und Kulturellen Standpunkte. Berlin.
Cash and Hopkinson. 1905. The British Freshwater Rhizopods and Heliozoa Ray Society. London.
Craig, C. F. 1912. The Parasitic Amoebae of Man.
Doflein, F. 1911. Lehrbuch der Protozoenkunde. Jena.
Penard, E. 1890. Études sur les rhizopodes d'eau douce. Mém. de la Soc. de Phys. et de l'histoire nat. de Génève. Tome 31.
Penard, E. 1902. Faune rhizopodique du bassin du Leman. Génève.
Wülkr, G. 1911. Die Tecknik der Amöebenzuchtung. Cent. f. Bakt. Nos. 19, 21.

Genus AMOEBA, Bory.

Rösel von Rosenhof in 1755 described a small organism under the name of "der kleine Proteus." The value of his description was recognized by Linnaeus, who gave to the organism the name *Volvox chaos*. Pallas also distinguished it under the name of *Volvox proteus*, while Bory de Saint Vincent in 1824 gave to it the generic name Amiba, which Ehrenberg in 1831 changed to its modern form Amoeba. Many recent writers have discarded the "o" and spell it Ameba, but their only justification would be to return to the original form and spell it Amiba.

The type form of the genus is *A. proteus* of to-day, which corresponds with Ehrenberg's *A. princeps* and with Rösel's kleine Proteus.

Generic characters.—Free living rhizopods, usually of large size (up to 1 mm. in diameter), with one or many nuclei and one or more contractile vacuoles. The protoplasm is differentiated into ectoplasm and endoplasm, pseudopodia forming from both parts or only from ectoplasm. The nuclei are large, with thick doubly refracting membranes and with chromatin concentrated in a single large karyosome or in granular form distributed throughout the nucleus. Reproduction by division and sporulation.

Amoeba proteus Pallas.

Synonyms:

Der kleine Proteus, Rösel von Rosenhof, 1755.
Volvox proteus, Pallas, 1766.
Amiba divergens, Bory de St. Vincent, 1822.
Amoeba princeps, Ehrenberg, 1831, 1838.
Amoeba proteus, Leidy, 1878, 1879.
Amoeba radiosa, Ehrenberg, 1830, 1831, 1838.

Leidy, J. 1878. Proc. Ac. Nat. Sc., Philadelphia.
Leidy, J. 1879. Fresh Water Rhizopods of North America, Washington.
Awerinzeff, S. 1904. Ueber die Theilung bei Amoeba proteus. Zool. Ans. Bd. 27.
Calkins, G. N. 1907. The Fertilization of Amoeba proteus. Biol. Bull., vol. 13.
Metcalf, M. M. 1910. Studies on Amoebae. Jour. Exper. Zool., vol 9, No. 2.

Prandtl, H. 1907. Die physiologische Dégeneration der Amoeba proteus. Arch. f. Prot. Bd. 8.
Scheel, R. 1899. Beiträge zur Fortpflanzung der Amöben. Festchr. von K. v. Kupffer, Jena.
Schubotz. 1905. Beiträge zur Kenntnis der Amoeba blattae u. A. proteus. Arch. f. Prot., vol. 6.

Large fresh-water form from 300–600μ. The ectoplasm is clearly defined, the endoplasm granular and vacuolated and takes part in the formation of the lobose pseudopodia. The nucleus in vegetative stages is single and has a thick membrane, chromatin usually in the form of granules. The contractile vacuole is large and definite, opening to the outside at the posterior end of the organism in motion. Reproduction by division and sporulation. Gametogeny preceded by the multiplication of nuclei, formation of secondary conjugating nuclei and development of secondary reproductive cysts (Calkins). The swarmers are amoeboid (Scheel). Young cells with stellate form formerly known as *A. radiosa*. Food, small animals, algae, diatoms, other protozoa, etc. Not viable on protozoan agar or other media. Common in fresh-water ponds and ditches among dead leaves and other detritis.

NOTE.—The process of gametogeny as described by Calkins has been criticized by Prandtl, Schubotz, Dobell, and others on the ground that the structures described were stages in the development of parasites. Scheel and Metcalf have confirmed my observations in part, but have not seen the identity, possibly because of the poor figures in my original paper. After careful comparison of amoebae parasitized by Nucleophaga and by the form described by Prandtl under the name "Allogromia," I find no reason whatsoever for changing my views regarding autogamy as originally described.

A. vespertilio Penard.

Penard, E. 1902. Faune rhizopodique du Bassin du Leman. Geneve.
Doflein, F. 1907. Studien zur Naturgeschichte der Protozoen. V. Amöbenstudien. Arch. f. Prot. Suppl. 1, 1907.

Common fresh-water form from 200–300μ. In motion the pseudopodia are usually pointed and triangular in outline; at rest they are radially arranged and often very long and thin. The nucleus is spherical, containing a globular karyosome in which the bulk of the chromatin is massed, and a peripheral substance containing little chromatin. Reproduction by fission in rounded forms in which the long pseudopodia are replaced by small papilliform processes. The karyosome divides by "mitosis;" a cell division following after a longer or shorter time. The resting cysts are globular with a thin gelatinous membrane. Multiple agamous reproduction sometimes occurs within the cysts in which the nucleus divides three times, resulting in the formation of eight young amoeboid forms. Sexual processes not known. Habitat pools and ponds similar to that of *A. proteus*. Not viable.

A. flava Greeff.

Greeff, R. 1891. Ueber die Erdamöben. Sitz. Ber. d. Ges. zu Bef. de Ges. Wiss. zu Marburg.

Möbius, K. 1888. Bruckstücke einer Rhizopodenfaune der Kieler Bucht. Abh. d. Berlin Akad. Wiss. Bd. 49.

Schepotieff, A. 1910. Amöbenstudien, Zool. Jahrb. Anat. Bd. 29, p. 485.

Large salt-water amoeba up to 1 mm. in length; young forms uninucleate; old forms multinucleate. The pseudopodia of young forms are short and radial in arrangement; protoplasm finely granular with peripheral ectoplasm and brownish-colored endoplasm, the latter taking no part in pseudopodia formation. Pellicle absent. The single nucleus has a doubly-refracting membrane, chromatin in the form of fine granules and with a central karyosome. This is the type studied by Greeff, by Gruber, and by Möbius. The nucleus divides by mesomitosis with the formation of nuclear plate at times; details not known.

The small uninucleate form grows and the nuclei divide until in the large forms they number from 45–80. These then fragment to form chromidia and the cell encysts. The cysts are oval or spherical from 500–525μ in diameter and of brownish-black color. The cyst wall is opaque and consists of two layers—an outer layer rough and warty, and an inner smooth layer. The chromidia form secondary nuclei which become the nuclei of isogametes with one flagellum. These conjugate two by two (not actually observed), and the result of conjugation is the formation of a uninucleate copula or zygote which transforms into a young uninucleate amoeba (Schepotieff). Habitat, salt water, Naples.

A. verrucosa Ehr.

Synonyms:

Amoeba terricola, Leidy.

Amoeba striata, Leidy.

Amoeba sphaeronucleolus, Greeff.

Ehrenberg, C. G. 1838. Die Infusionsthierschen als volkommne Organismen. Berlin.

Gläser, H. 1912. Untersuchungen über die Theilung einiger Amöben. Arch. f. Prot. Bd. 25, p. 27.

Rhumbler, L. 1898. Physik. Analyse von Lebenserscheinungen der Zelle. Arch. f. Entwickl. Vol. 7, p. 103.

Fresh-water form much smaller than *A. proteus*, 80–100μ. It is a sluggish form with dense ectoplasm and a still denser pellicle. Its protoplasm is yellowish to white and transparent. Pseudopodia are few in number, forming a lamella-like process at one end. The pellicle is thrown into folds giving the characteristic striated appearance thus distinguishing it from other free living amoebae. The nucleus is relatively large, oval, or spherical in form, with a conspicuous karyosome and an ex-centric nucleolus. A single contractile vacuole is invariably present but the endoplasm has few vacuoles.

Nuclear division promitotic with pole bodies and central nuclear plate (Gläser). Reproduction by division the only known method of increase. This species is very close to if not identical with *A. terricola*, Greeff.

A. terricola, Greeff.

Similar to, if not identical with *Amoeba verrucosa*, Ehr.

Greeff, R. 1891. Ueber die Erd-Amoeben. Sitz. Ber. d. Ges. d. Naturwiss. zu Marburg.

Leidy, J. 1879. The Fresh Water Rhizopods of North America. Washington. Cash and Hopkinson. See No. 2.

Grosse-Allermann, W. 1909. Studien über Amoeba terricola. Arch. f. Prot. V. 17.

Sluggish form from 90–200μ similar in general characters to *A. verrucosa*. Its rhizopod characters are said to be difficult to determine owing to its slow movements and crystalline appearance. The pseudopodia are slow to form, very blunt and short. The ectoplasm and endoplasm are distinct, but the former is only a small zone about the cell which is bounded by a definite pellicle. The endoplasm is alveolar with large refringent granules or crystals. Nuclei are one or many in number and contractile vacuoles are numerous. The nuclei vary in size from 20–30μ with large and distinct karyosomes. Reproduction by fission and possibly by multiple division, but details are unknown. (See Gross-Allermann.) Habitat, moss.

In addition to these well-known amoebae there are others of allied type belonging to the genus Pelomyxa. These are large forms with many nuclei and with very sluggish movement without definite pseudopodia formation. Schaudinn's *Amoeba binucleata* is sometimes placed here.

Genus VAHLKAMPFIA CHATTON, emend Calkins.

Synonyms:

Nägleria (in part) Alexeieff.

Hartmannia (in part) Chatton.

Alexeieff, A. 1912. Sur les caractères cytologiques et la systematique des Amibes du groupe limax (Nägleria nov. gen. et Hartmannia nov. gen.), etc. Bull. de la Soc. Zool. de France, vol. 37, No. 2.

Chatton, E. 1912. Sur quelques genres d'amibes libres et parasites. Synonymies, homonomie, Impropriété. Bull. d. la. Soc. Zool. de France, vol. 37, No. 8.

Chatton and Lalung-Bonnaire 1911. Amibe limax (Vahlkampfia nov. gen.) dans l'intestin humain. Bull. de la Soc. de Path Exot., vol. 5, p. 135.

For reasons given in the introduction we follow Chatton in placing some of the forms belonging to the " limax " group and included generally in the old genus Amoeba, in a new genus named after Vahlkampf who first accurately described one of this miscellaneous collection. We find it necessary, however, to limit the genus somewhat more narrowly than does Chatton, by eliminating those types with the capacity to change from amoeboid into flagellated forms and

vice versa. These types we place in Alexeieff's genus Nägleria characterizing the genus Vahlkampfia as follows:

Minute free-living or commensal rhizopods moving as a finger-formed single pseudopodium or with irregular ectoplasmic outbursts to form a local or general hyaline ectoplasm. The nucleus is single or double with finely divided chromatin forming a membrane-like contour and with a definite karyosome. Reproduction by simple division, the karyosome dividing first like the nucleolus-centrosome of Euglena, the peripheral chromatin forming the nuclear plate (promitosis of Nägler). Cysts uninucleate. Food bacteria; habitat usually fresh water in ponds, etc., but many types are found in garden earth and some may be marine.

Vahlkampfia limax Duj. emend Vahlkampf.

Synonyms:

Amoeba limax Dujardin.

Amoeba limax of authors in part.

Alexeieff, A. 1912. See preceding bibliography.

Chatton, E. 1910. Essai sur la structure du Noyau et la mitose chez les Amoebiens. Arch. d. Exper. et Gen. Tome 5. No. 6.

Dujardin, F. 1841. Les Infusoires in Suites de Buffon. Historie naturelle des zoophytes.

Minute form from 3–4μ in length and 0.75μ in width. Movement in a zigzag manner by the formation of pseudopodia first on one side, then on another in the general direction of movement. The anterior end during movement is broader than the posterior end. There is no differentiation into ectoplasm and endoplasm, except where the pseudopodia are forming. One contractile vacuole is present in the posterior part of the cell and is distinctly visible. The nucleus is single, visible in the living cell, and from 0.3–0.5μ in diameter. When stained the nucleus shows a membrane lined by chromatin, a colorless zone within the membrane and a distinct spherical karyosome in the center. At division this karyosome first elongates then constricts in the middle and divides, the nuclear plate being formed from the peripheral chromatin. The colorless zone forms an elongated matrix in which indistinct fibers ultimately appear. The daughter plate chromatin collects in a mass on one side of the daughter karyosome and then breaks up to form the peripheral layer around the membrane. The cysts are spherical, uninucleate and about 1.5μ in diameter. The cyst wall is brown in color but transparent. Contractile vacuole absent. Viable.

Vahlkampfia paedophthora Caullery.

Synonym: ***Amoeba paedophthora*** Caullery.

Caullery, M. 1910. Sur un amoebien parasite des embryons de Peltogaster curvatus Kossa. C. R. Soc. Biol. de Paris Tome 61.

Small form parasitic in the eggs of Peltogaster a crustacean. Endoplasm highly vacuolated, nucleus minute with distinct karyosome.

Division promitotic. Said to be an active agent in the destruction of eggs and embryos of the crab.

V. froschi Hartmann.
Synonym: *Amoeba froschi* Hartmann.
Hartmann und Prowazek, 1907. Blepharoplast, Karyosom, und Centrosom. Arch. f. Prot. Bd. 10.
Gläser, H. 1912. See bibliography, p. —.
Nägler, K. 1909. Entwicklungsgeschichtliche Studien über Amöben. Arch. f. Prot. Bd. 15, p. 1.

Small forms usually from 8–12μ in diameter. Nucleus from 1–2μ. Movements similar to those of *V. limax*. The nucleus is central without a firm membrane and with a distinct karyosome and centriole. Gläser interprets the latter as only a part of the karyosome which retains the stain longest and does not regard it as a definite body. Its independent division, however, seems to show that it is quite as independent as the centrosome of higher cells. Nuclear division is slightly different from that of *V. limax* by reason of the concentration of chromatin in the karyosome. Nuclear plate, polar masses, and reconstruction are similar to those of limax, the division therefore is promitotic. The cysts are spherical, from 7–10μ and with double membrane. Sexual processes said to be autogamous (Nägler).

V. lacustris Nägler.
Synonym: *Amoeba lacustris* Nägler.
Nägler, K. 1909. See preceding bibliography.

Minute forms, from 8–15 μ with only slight differences from other limax forms. The small peculiarity of the nuclear plate in division does not seem to us a sufficient characteristic for a distinct species, and until its life history is made out this form should be considered only a variant of *V. limax*. The cyst is uninucleate, transparent, and without marked characteristics. Fresh water.

V. lacertae Hartmann.
Synonym: *Entamoeba lacertae* Hartmann, 1907.
Hartmann und Prowazek, 1907.
Nägler, K. 1909. See above.

Small form, from 10–20 μ in diameter, with highly vacuolated cytoplasm and distinctly visible nucleus. The karyosome is surrounded by a peripheral row of chromatin granules which fuse to form larger masses bound together by a fine reticulum. A centriole is plainly seen even in the living state. Nuclear division is promitotic. The cysts are smaller than the vegetative forms and have no marked characteristics beyond a slightly wrinkled outer membrane. Habitat, commensal in the gut contents and cloaca of lizards. Viable.

V. albida Nägler.
Synonym: *Amoeba albida* Nägler.
Nägler, K., 1909. Entw. Studien über Amoeben. Arch. f. Prot. Bd., 15, p. 24.

Larger form characterized by a hyaline or transparent cell body, slow movements, and distinct nuclear membrane, from 20–40 μ. Divi-

sion of the nucleus promitotic. Sexual processes autogamic, with tetrad-like fertilization nuclei. Habitat, garden earth. Viable.

V. horticola Nägler.

Synonym: *Amoeba horticola* Nägler.

Nägler, K., 1909. See preceding bibliography.

Small form, from 15–25 μ in diameter. Movement by protrusion of long pseudopodia; ectoplasm and endoplasm distinct, the latter with large granules and smaller refractive bodies and single contractile vacuole, difficult to see because of the granules. The nucleus, visible in the living cell, has a large karyosome surrounded by a hyaline zone. The division is promitotic, with centrioles. The chromatin of the nuclear plate is said to differ from that of other limax forms in being concentrated into six definite chromosomes. Cysts are 10 μ in diameter, somewhat ellipsoidal in form. Sexual processes unknown. Habitat, garden earth. Viable.

V. diploidea Hartmann and Nägler.

Synonyms:

Sappinia diploidea Alexeieff, 1912.

Hartmannia Chatton, 1912.

Hartmann u. Nägler, 1908. Kopulation bei Amoeba diploidea mit Selbstandigbleiben der Gametenkerne während des ganzen Lebenscyclus. Sits. Ber. d. Ges. Nat. Fr. Berlin, 1908.

Small forms, from 15–30 μ in diameter; ectoplasm with distinct pellicle; nucleus double in the vegetative stages, each with karyosome and peripheral chromatin, and division is synchronous, promitotic in type. Conjugation occurs by fusion of two amoebae within a common cyst, the two nuclei in each cell now uniting, the fused nuclei forming the two nuclei of the vegetative stages. Habitat, garden earth. Viable.

V. mucicola Chatton.

Chatton, E., 1909. Une Amibe, Amoeba mucicola n. sp., parasite des branchies des labres. C. R. Soc. Biol de Paris. Tome 67.

Small forms, from 12–30 μ, with highly vacuolated endoplasm and limax-like ectoplasm. Nucleus visible as a clear vesicle, with a distinct karyosome. Contractile vacuole not observed. Nuclear membrane limax-like. Division promitotic. Habitat, ectoparasitic on fish at Banyuls.

V. polypodia Schultze.

Synonym: *Amoeba polypodia* F. E. Schultze.

Schultze, F. E., 1875. Rhizopodenstudien, V. Arch. mik. Anat. Bd. 2.

The identity of this amoeba is somewhat questionable and it has been accepted generally as a type which reproduces by direct division. Renewed study, however, with modern methods would probably show that it belongs to the limax type of promitosis, since Schultze described a hyaline zone around the highly refractive "nucleus" (karyosome?). His observations were made solely on the living cell and

the chromatin and nuclear plate were probably not seen. The ray-like pseudopodia, however, are characteristic.

V. tachypodia Gläser.

Synonym: *Amoeba tachypodia* Gläser.

Gläser, H., 1912. Untersuchungen über die Theilung einiger Amöben. Arch. f. Prot. Bd. 25.

Small form, from 15–30 μ, which Gläser regards as a variety of limax varying from the latter in ectoplasmic and nuclear structures. One contractile vacuole; nucleus visible in life surrounded by a definite membrane and containing a hyaline zone, in the center of which is the karyosome. Movement rapid and form changes constant. Cysts from 10–11 μ, similar to those of limax. Nuclear division promitotic, the karyosome dividing by lateral constriction; nuclear plate with large chromatin granules. Habitat, pond or lake water. Viable.

V. lamellipodia Gläser.

Synonym: *Amoeba lamellipodia* Gläser.

Gläser, H., 1912. See preceding bibliography.

Larger forms, from 25–50 μ in length and 10–18 μ in width; ectoplasm clearly defined about the entire cell, giving the impression of a lamella; endoplasm highly vacuolated and filled with refractive granules; contractile vacuoles numerous. Nucleus distinct in life; no protective cysts in water. In agar cultures cysts sometimes appear, easily recognizable by the collection of deeply refractive granules about the nucleus. Nuclear division is preceded by enlargement of the karyosome, which becomes vacuolated, while the zone about it becomes filled by a fine chromatic reticulum. The karyosome finally resolves into an achromatic spindle, with distinct chromosomes forming the nuclear plate. Pole bodies are absent, division therefore mesomitotic. Habitat, pond water. Viable.

V. binucleata Gruber.

Synonyms:

Amoeba binucleata Gruber.

Pelomyxa binucleata Doflein, 1911.

Sappinia binucleata Alexeieff, 1912.

Gruber, 1884. Studien über Amöben. Zeit. wiss. Zool. Vol. 41, p. 208.

Schaudinn, F., 1895. Ueber die Theilung von A. binucleata. Sit Ber. Ges. Nat. Fr. Berlin. Bd. 6, p. 130.

Larger form with double nuclei, which divide by synchronous mesomitosis. Life history unknown, possibly a stage in the development of Pelomyxa, with which it is found. Habitat, pond water.

V. guttula Dujardin.

Synonyms:

Amoeba guttula Dujardin, 1841.

Amoeba platypodia Gläser, 1912.

Dujardin, F., 1841. Histoire naturelle des zoophytes. Infusoires.

Larger forms, from 30–50 μ, with highly transparent protoplasm; one contractile vacuole at the posterior end; ectoplasm distinct.

Nucleus with great karyosome distinctly visible in life. Protective cysts absent. Nuclear division mesomitotic similar to that of *A. lamellipodia*, but the anaphase is characterized by the collection of chromatin into large polar masses resembling *V. limax*. Habitat, pond water. Viable.

This is the same species evidently as the one described by Gläser under the name *A. platypodia*, which is somewhat smaller (13–25 μ), and has a wider ectoplasm.

Genus NÄGLERIA, Alexeieff (emend Calkins).

Synonyms:

Amoeba limax Alexeieff.
Vahlkampfia species Chatton.

This genus, including a number of limax forms, was established by Alexeieff to include all of the questionable minute amoeboid forms which Chatton earlier included in his genus Vahlkampfia. Amongst these, however, were some species in which the life history on agar involved a change from the amoeboid to the flagellated stage, and vice versa. This is a distinct characteristic of generic value, and until similar flagellated stages are demonstrated in all species of Vahlkampfia they should be kept separate in classification. I have adopted Alexeieff's generic name, therefore, to include these limax forms, with a facultative flagellated stage.

Whitmore (1911) still earlier described an amoeba from Manila with a flagellated stage in which three flagella were present. He named it *Trimastigamoeba philippinensis*. It is unfortunate that such a generic name should have been given to this type, for in the first place it is not a mastigamoeba (which is the generic name of a flagellate), and in the second place the prefix makes it inapplicable to the biflagellated types. Hence we must include it as a subgenus provisionally or else place the biflagellated forms under the inappropriate name of Trimastigamoeba. It may be better in the long run to place all amoeboid forms with flagellated stages under one generic name, in which case both Trimastigamoeba and Nägleria would be supplanted by Schaudinn's name Paramoeba. Until the life history of more species is fully known I think the latter course inadvisable, and will treat the uniflagellate, biflagellate, and triflagellate forms as different genera.

Generic characters.—Small limax-like forms with no essential morphological differences from Vahlkampfia, except for the fact that the adult amoebae acquire and lose flagella under conditions not fully recognized. They are viable, possess one contractile vacuole and a single nucleus of the limax type. The flagellated stage with definite oval form. Nuclear division promitotic; division of the flagellate stage unknown in the majority of cases.

Nägleria punctata Dangeard.

Dangeard, P., 1910. Etudes sur le developpement et la structure des organismes inferieurs. Le Botaniste Vol. 2.

Wasielewsky und Hirschfeld, 1910. Untersuchungen über Kulturamöben. Abh. Heidelberg. Ak. Bd. 1.

With the characters of the genus. Size about 25μ; nucleus with a distinct karyosome; flagella two in number, equal in length and about as long as the cell body. The nucleus of the flagellated forms is at the anterior end of the cell near the base of the flagella, while the contractile vacuole is posterior. Cysts uninucleate, smaller than the adults. Division promitotic. Habitat pond water.

Wasielewsky and Hirschfeld, 1910, have described somewhat similar flagellated stages in an amoeba from hay and in one from tan bark.

Genus Paramoeba Schaudinn.

Schaudinn, F., 1896, Ueber die Zeugungkreis von Paramoeba Eilhardi.

This genus was created by Schaudinn for an amoeba found by him in a salt-water aquarium. It is characterized by a peculiar relation of nucleus and accessory body which Schaudinn called the Nebenkörper. The latter divides first into many parts and then the nucleus divides into as many parts as there are portions of the Nebenkörper. The genus is further characterized by the formation of swarmers with two flagella, two chromatophores and a pigmented "eye-spot" or stigma. The flagellates increased by longitudinal division recalling in morphology and division the small flagellate Cryptomonas. The observations need confirmation. *Paramoeba eilhardi* Schaudinn. The single species known, with the characters of the genus.

Genus Craigia Nov. gen.

Craig, 1906, observed a small amoeba in the human intestine in six cases of chronic diarrhoea. He named it *Paramoeba hominis* because of the presence of an accessory body which he compared with the Nebenkörper of *P. eilhardi* and the formation of flagellated swarmers. The identity of the accessory body with the Nebenkörper is questionable while the single flagellum of the swarmers is sufficient to throw it out of the genus named by Schaudinn. For these reasons I propose to give it a new generic name—Craigia—after its discoverer.

Generic characters.—Small, free-living or parasitic amoebae with a uniflagellated swarmer stage. Amoeba stage from 10–25μ with little differentiation into ectoplasm and endoplasm when quiet but with anterior ectoplasm in movement. The endoplasm with or without an extranuclear body recalling the Nebenkörper of Paramoeba. The flagellated stage with a single flagellum.

C. hominis Craig.

Synonym: *Paramoeba hominis* Craig.

Craig, C. F., 1906. In Amer. Jour. of the Med. Sciences, 1906.

Craig, C. F., 1910. Further Observations on Paramoeba hominis, an Intestinal Parasite of Man. Arch. of Intern. Med. Vol. 6, p. 1.

With the characters of the genus. Endoplasm granular with accessory body interpreted by Craig as Nebenkörper, but this is not satisfactorily demonstrated. Flagellated form smaller than the amoebic stage (10–20μ), spherical with slight conical protuberance at the base of the flagellum. Multiplication of the flagellates by longitudinal division including division of the motile organ. Cysts from 15–18μ in diameter, spherical, with the usual double membrane. Reproduction by simple division in amoebic and flagellated stages, and by swarmer-formation within the cysts. Habitat human intestine, where it possibly causes a chronic diarrhoea. Confirmation needed.

C. pigmentifera Grassi, 1881.

Synonym:

Paramoeba pigmentifera Janicki.

Amoeba pigmentifera Grassi.

Grassi, G. B. See following bibliography.

Janicki, C. See following bibliography.

Small forms only 30μ in diameter. Movement slow, endoplasm highly granular, ectoplasm visible only at point of pseudopodia formation. The nucleus is difficult to see in life. Nebenkörper larger than the nucleus and covered with a black pigment. Flagellate stage with a single flagellum, Nebenkörper and nucleus. As in Paramoeba eilhardi the flagellates reproduce by division (Janicki). Body cavity of Chaetognatha.

C. chaetognathi Grassi.

Synonyms: *Amoeba chaetognathi* Grassi. Paramoeba chaetognathi Janicki.

Grassi, G. B., 1881. Intorno ad alcuni protisti endoparassitici, etc. Atti Soc. Ital. Sc. Nat. Vol. 24.

Janicki, C., 1912. Untersuchungen an parasitischen Arten der Gattung Paramoeba Schaudinn. Verh. d. Naturf. Ges. in Basel. Bd. 23.

Smaller form than the preceding (18μ). Protoplasm and inclusions similar to those of the preceding. Nebenkörper not visible in life. Flagellate stage similar to the preceding. Life history unknown. Body cavity of Chaetognatha.

Genus TRIMASTIGAMOEBA Whitmore.

Single species *T. philippinensis* Whitmore.

Whitmore, E. R., 1911. Studien über Kulturamöben. Arch. f. Prot. Vol. 23, p. 81.

Amoeboid form of limax type from 16–18μ in diameter. Ectoplasm not distinct from endoplasm, except in advancing pseudopodium. Contractile vacuole present in posterior end of body. Ordinary vege-

tative forms change into flagellated forms. The latter have three equal flagella, are oval and elongate from 16–22μ in length with nucleus in the anterior end. Habitat tap water, Manila.

Genus ENTAMOEBA, Leidy.

Synonyms:

Amoeba Loesch.
Endamoeba Leidy.
Entamoeba Casagrandi and Barbagallo.
Löschia Chatton.
Proctamoeba (Alexieff) (in part).

The present genus was established by Leidy in 1879, although with slightly different orthography, the name given by him being Endamoeba. The significance is identical, and Leidy therefore should have credit for the name. In this country we use the form *end* rather than *ent* for terms like endoderm, endoplasm, etc., while in Europe the form is entoderm, entoplasm, etc. Without considering the academic question as to which form is the more accurate, the fact remains that endamoeba was the original name, Casagrandi and Barbagallo in 1897 using the form entamoeba without reference to Leidy's priority. We agree with Chatton therefore in crediting Leidy with the generic name, but accept the form given by Casagrandi and Barbagallo and adopted by Schaudinn.

A great deal of *a priori* reasoning has been invoked to prove that all pathogenic and parasitic forms of amoeba are not viable on protozoan agar or other culture media, while, on the other hand, cultivated forms from diseased entera are often dismissed as being free-living forms which in the encysted state have passed through the alimentary tract without entering upon the vegetative stages. On purely a priori grounds, however, and with the possible exception of *E. histolytica* and *tetragena*, there is no reason why parasitic forms should not be cultivated on agar. Nor, on the other hand, is there any reason why free-living forms should not become adapted to life on bacteria in the digestive tract, since this is the only obvious way in which pathogenic forms originally must have acquired their parasitic mode of life. We must seek some other means than viability for identifying parasitic and pathogenic forms from those which are normally free living, and here, as in all other kinds of protozoa, the full life history must first be known. In lieu of this, the differences in morphology, especially of nuclei, mitotic figures, and crysts may be provisionally accepted.

Generic characters.

Commensal, parasitic, or pathogenic amoeba living a vegetative life in the digestive tracts of different animals from man to lower invertebrates. Size usually small (from 10 to 50μ); ectoplasm more or less well defined; endoplasm clear, or finely granular, or with large granules of volutin, or with chromidia. Contractile vacuoles

usually absent. Nuclei vesicular with or without definite karyosomes. Nuclear division mesomitotic or mitotic. Reproduction by simple division, by budding, or by spore formation. Life history known in only a few forms; sexual processes autogamic when known. Commensal forms probably viable; cytolytic forms probably not.

Type species *Entamoeba blattae* Bütschli, 1878.

Bütschli, O. 1878. Beiträge zur Kenntnis der Flagellaten u. einiger verwandten Organismen. Zeit. wiss. Zool. Bd. 30, p. 205.

Elmassian. 1909. Sur l'Amoeba blattae. Morphologie, Generation. Arch. f. Prot. Bd. 16, p. 143.

Janicki, C. 1908, Contrib. alla canoscenza di alcuni Protozoi parassiti della Periplaneta orientalis. Atti d. Reale Acad. dei Lincei. Vol. 17.

Janicki, C. 1909. Ueber Kern und Kerntheilung bei Entamoeba blattae Büt. Biol. Cent. Vol. 39, p. 381.

Leidy, J. 1879. On Amoeba blattae. Proc. Ac. Nat. Sc. Philadelphia, Oct., 1879.

Mercier, L. 1909. Le cycle évolutif d'Amoeba blattae Büt. Arch. f. Prot. Bd. 16, p. 165.

Mercier, L. 1910. Beiträge zur Kenntnis der Amoeba blattae u. A. proteus. Arch. f. Prot. Bd. 6, p. 1.

Single individuals from 12–50μ, but may become much larger (80–100μ). The living forms show little evidence of ectoplasmic differentiation, but the endoplasm is marked by fairly definite striations. The single nucleus has a definite peripheral layer of chromatin and a small karyosome. Multinucleate forms are also common. Contractile vacuoles numerous. Transparent multinucleated cysts are formed with from 20–30 nuclei. According to Mercier, these are gamete-forming cysts which give rise to minute uninucleate gametes which conjugate outside the cyst, the copula developing into the ordinary vegetative forms. Vegetative reproduction by simple division. Habitat, end gut of various species of cockroaches.

E. ranarum Grassi, 1881.

Synonym: *Amoeba ranarum* Grassi.

Dobell, C. C. 1909. Researches on the intestinal parasites of frogs and toads. Q. J. M. S. Vol. 53, n. s.

Grassi, G. B. 1881. See bibliography p. —.

Size variable from very minute forms (buds ?) 3–5μ up to a medium size of 20–40μ and occasionally 60μ. Movement similar to that of limax forms. Protoplasm very fluid with many vacuoles and with one spherical nucleus. Reproduction by simple division or by spore formation within a cyst, four spores being formed (Dobell). Hartmann describes an autogamous sexual cycle. Habitat stomach to end gut of frogs.

E. testudinis Hartmann.

Hartmann, M. 1910. Ueber eine neue Darmamoebe. E. testudinis. Mem. do Instituto Oswaldo Cruz. Vol. 2.

Size from 50–70μ. Ectoplasmic differentiation distinct. Endoplasm filled with vacuoles and food particles in various stages of diges-

tion. Nucleus visible in life, from spherical to oval shape, with fine peripheral granules of chromatin, central spongy mass corresponding to a karyosome, and a distinct nuclear membrane. Reproduction unknown. Habitat, digestive tract of turtle.

E. buccalis Prowazek.
Synonyms:
Amoeba buccalis Steinberg.
Amoeba pulmonalis Artault.

Prowazek, P. 1904. Entamoeba buccalis. Arbeit. a. d. Kais. Gehundheits. Bd. 21.
Leyden, 1905. In Löwenthal Entamoeba buccalis Prow. in einem Fall von Carcinom des Mundbodens. Charité Annalen Bd. 29.

Small active forms from 6–32μ. Ectoplasm and endoplasm differentiated when organisms are at rest. Endoplasm filled with gastric vacuoles; contractile vacuole absent. Nucleus small, with karyosome, centriole and peripheral chromatin. Nuclear division evidently promitotic, but not sufficiently studied for definite statement. Spore formation probable. Habitat carious teeth; also found in mouth carcinoma, and possibly in lungs (Artault 1898, *A. pulmonalis*).

E. Kartulisi Doflein.
Synonym: *E. maxillaris* Kartulis.

Doflein, F. 1901. Die Protozoen als Parasiten und Krankheitserreger.
Doflein, F. 1911. Lehrbuch der Protozoenkunde.

Size from 30–38μ. Ectoplasm not clearly differentiated; endoplasm filled with large granules. Movement active with long finger formed pseudopodia recalling the "tentacles of a snail." Nucleus small with definite karyosome, not visible in life. Contractile vacuole absent. Reproduction unknown. Habitat, man; first found in a tumor of the lower jaw in Egypt (Kartulis) and in America (Flexner). The organisms occur not only in the abscess fluid but also in the deeper bony tissues. Possibly related to *E. histolytica*.

E. urogenitalis Baelz.

Bälz, 1883. In Berliner klin. Wochenschr., p. 237.
Jurgens, 1892. In Deutsch. mediz. Wochenschr., p. 454.
Kartulis, 1893. Ueber pathogene Protozoen bei dem Menschen. Zeits. Hyg. und Inf. Bd. 13, p. 2.
Posner, 1893. Ueber Amöben im Harn. Berlin Klin. Wochenschr. Bd. 30, p. 674.

Size from 22–50μ. Movement slow by means of short pseudopodia. Endoplasm highly granular with one or more nuclei. Red-blood corpuscles also found in endoplasm. Reproduction unknown. Habitat mucous membrane of the human bladder. Possibly related to *E. histolytica*.

E. histolytica Schaudinn.
Synonym: *Amoeba dysenteriae* Councilman and Lafleur.
Schaudinn, F. 1903. See bibliography p. —.
Craig, C. F. 1912. See below p. —.

Since Councilman and Lafleur's description of "*Amoeba dysenteriae*" was inadequate to enable us to distinguish to-day the organism with which they worked, we accept the subsequent names "histolytica" and "tetragena" given by Schaudinn and Viereck. This was the first amoeba to be distinguished as pathogenic from the harmless *E. coli* by the careful observations and experiments of Schaudinn. Like *E. tetragena*, it is a cause of pernicious or tropical dysentery.

Many recent observers claim that *histolytica* and *tetragena* are the same; others, notably Craig, find a distinct difference in appearance and life history.

Size from 20–30μ (Doflein), 10–70μ (Craig). Movement active by means of blunt or finger formed pseudopodia which are refractive and clearly distinguished from the rest of the cell. Endoplasm granular and contains numerous vacuoles and ingested red-blood corpuscles when the latter are present in the fæces. Contractile vacuole absent. Nucleus difficult to see in life, contains but little chromatin, and has a minute karyosome. It is ex-centric in position, usually lying against the cell membrane. A definite nuclear membrane is absent. Reproduction by simple division, by budding, and by permanent spore formation. The latter are formed by budding, contain chromidia and are covered by a brown cyst wall. Life history still unknown. Habitat, human digestive tract, causing acute enteritis and abscess formation in various organs.

E. tetragena Viereck.
Synonyms:
Entamoeba africana Hartmann.
Viereckia tetragena Chatton.

Chatton, E. et Lalung-Bonnaire 1912. Amibe limax (Vahlkampfia n. gen.) dans l'intestin humain. Bull. de la Soc. de Path. Exot. Vol. 5, p. 135.
Craig, C. F. 1911. Entamoeba tetragena as a cause of Dysentery in the Philippine Islands. Arch. of Intern. Med. Vol. 7, p. 362.
Hartmann and Prowazek. 1907. Blepharoplast, Karyosom und Centrosom. Arch. f. Prot. Bd. 10. p. 312.
Viereck, H. 1906. Ueber Amöbendysenterie. Med. Klinik. 1906. No. 41.
Viereck, H. 1907. Studien über die den Tropen erworbene Dysenterie. Arch. f. Schiffs. und Tropenhyg. Bd. 2. Beiheft 1.

According to recent research this seems to be the most common cause of tropical dysentery. It measures from 8–60μ, has lobose or finger-formed pseudopodia, which are distinctly refractile and well differentiated from the rest of the cell. Endoplasm granular and contains red-blood corpuscles when the latter are present in the fæces. The nucleus is distinctly visible in life and has a definite

double-contoured membrane lined by chromatin. A large karyosome is present and a distinct centriole. Reproduction by simple division and by spore formation preceded by autogamous fertilization. The result of fertilization is the formation of cysts with four amoeboid uninucleated spores. The latter number is the chief distinguishing feature between tetragena and E. coli, the latter having eight spores. The vegetative characters are so similar to those of *E. histolytica* that, until the life history of the latter is known, some doubt must still remain as to its specific difference. If this history shows identity between the two, then the name *tetragena* must be abandoned and *histolytica* retained. Habitat, human intestine, causing acute tropical dysentery.

E. coli, Lösch, emend Schaudinn.

Synonyms:

Amoeba coli Lösch.

Amoeba lobospinosa Craig.

Casagrandi and Barbagallo, 1897. Entamoeba hominis, etc. Ann. Ig. sperim. Vol. 5, p. 103.

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Average size from 25–35μ, but varies from 7–70μ. Movement is sluggish by protrusion of small blunt pseudopodia not well differentiated from the rest of the cell. General appearance glassy or transparent and with a gray tone. The endoplasm is finely granular with noncontractile vacuoles. Reproduction by simple division, or by multiple division, in which the nucleus fragments into eight parts, each part becoming the nucleus of an amoeboid spore. Fertilization autogamous, resulting in cyst formation, each cyst containing eight nuclei. After infection of a new host these amoeboid germs emerge from the cyst as minute amoeboid swarm spores. The cysts measure about 15μ. Habitat, human intestine, where, as a harmless commensal, it lives on bacteria.

E. muris Grassi.

Synonym: *Amoeba muris* Grassi.

Grassi, G. B. 1881. See bibliography p. —.

Wenyon, C. W. 1907. Observations on the Protozoa in the Intestine of Mice. Arch. Prot. Suppl. 1, p. 169.

Small forms up to 40μ. Movement slow or rapid, according to temperature. Pseudopodium formation of the limax type. Ectoplasmic layer narrow and distinctly visible only in the pseudopodium. Endoplasm granular with large gastric vacuoles containing a variety

of food matters. Nucleus visible in life; it is spherical and has a thick membrane. The chromatin is scanty and distributed as granules about the periphery. A karyosome lies in an achromatic network. Reproduction by division and by sporulation within cysts. The latter are spherical or oval, from 12–14μ in diameter. Maturation and autogamous fertilization occur within the cyst, resulting in eight nuclei, which probably form the nuclei of eight spores. Habitat, intestine and coecum of the mouse.

E. Intestinalis Walker, 1908.

Walker, E. L. 1908. See below.

Williams, A. W. 1911. Pure Cultures of Amoebae parasitic in Mammals, Jour. Med. Res. Vol. 25, p. 263.

Medium-sized forms of the coli type. Ectoplasm and endoplasm distinct; nucleus with large karyosome which furnishes the chromatin of the nuclear plate. Division of the nucleus mesomitotic. Highly phagocytic, red-blood corpuscles taken up with avidity. Reproduction by division and by budding. Life history unknown. Habitat, intestine of rabbit and dog. Viable.

E. cobayae Walker, 1908.

Walker, E. L. 1908. The parasitic Amoebae of the Intestinal Tract of Man and other Animals. Jour. Med. Res. Vol. 17, p. 445.

Similar in all respects to *E. intestinalis*. Habitat, intestine of guinea pig. Viable.

NOTE.—In the review of species given above it is probable that a number of types have been omitted or overlooked. If such is the case I apologize in advance and plead that no slight has been intentional, the absence of literature, especially in medical journals, making it impossible to cover the entire field in the short time at my disposal. A mere glance through the preceding pages shows the need of a modern and thorough monograph of the free and parasitic amoebae, and the writer will be very glad to undertake such a monograph if he can have the cooperation of the various students of the group.

THE CULTIVATION OF AMEBAE.

By Dr. GARY N. CALKINS,

Professor of protozoology, Columbia University, New York City.

The time is now past when one or a few individuals of protozoa suffice to justify the publication of a new species or a description of normal processes. To-day the protozoologist, no less than the cytologist working in cellular biology, must base his conclusions on vital activities or structural peculiarities of protozoa upon the study of

thousands of cells. To obtain these, "cultures" are necessary, and the development of cultural technique is one of the most recent lines of work in protozoology.

There is the greatest latitude in the use of the word culture as applied to protozoa. In general, it signifies an accumulation of one species under environmental conditions favorable for the active growth and multiplication of that species, but we frequently hear the term used to mean a rich collection of protozoa of many kinds. Very often we find, in natural waters or infusions, vast numbers of a single species; such "natural cultures" are eagerly sought by the protozoologist and quantities of "material" of Noctiluca or Peridinium in sea water, or of Colpidium, Paramecium, Vorticella, Spirostomum, Chilomonas, and other forms of ciliates and flagellates are thus obtained. Such "natural cultures," however, make of the protozoologist too much of an opportunist and "artificial culture" methods have been devised to supply the demand for quantities of material at will.

The secret of making artificial cultures consists in finding the appropriate food of the organism to be studied. When such food is the bacteria of pond water, for example, the problem is simple, and tens of thousands of Colpidium, Paramecium, Vorticella, Stylonychia, etc., can be raised from one individual in a few weeks. When the food is specific, the difficulty is greater. Then food habits must be studied and the specific food required raised in abundance. In this way we have learned to cultivate ciliated protozoa of many kinds—Didinium on Paramecium, Spathidium on Colpidium, Actinobolus on Halteria, etc.—through hundreds of generations.

It may be stated without exaggeration that probably every type of protozoa can be cultivated artificially, and this generalization applies in the case of our present subject, Amoeba. Experience has shown that with these rhizopods, as with the infusoria, some lend themselves readily to the culture methods, while others, thus far, have given negative results. This is true of the largest and finest specimens of amoebae, viz, *A. proteus*, *A. vespertilio*, *A. flava*, etc. Nevertheless, these forms frequently appear in great abundance in "natural cultures," and it is only a matter of time and research to discover the conditions under which they thrive.

Amoebae which have been cultivated on artificial media have been in all cases those forms which normally feed on bacteria. The methods of cultivation, especially in the hands of the bacteriologists, have become more and more perfected until now it is possible to obtain "pure cultures" of certain types. Williams (1911) distinguishes three types of amoeba cultures as 1, mixed cultures; 2, pure mixed cultures; and 3, pure cultures; and full accounts of the many methods that have been employed in getting such cultures may be found in

the works of Behla (1898), of Vahlkampf (1905), Musgrave and Clegg (1906), and Walker (1908).

Mixed cultures of amoebae have furnished material for study since the time of Auerbach, in 1856, but until comparatively recent years little effort was made to study a single species. This became possible when "pure mixed cultures" were used in which a single strain of amoeba was grown with a single species of bacteria as food. The great majority of papers on the cultivation of amoebae have been based upon this type of culture, which from the zoological standpoint is perfectly satisfactory. A common way of starting cultures of water-dwelling amoebae is to seed sterile straw or hay infusions with specimens of the amoeba desired. This was the method of Auerbach and the earlier investigators. A better way is to seed the desired amoebae on some gelatinous medium, such as agar or gelatine, to which sterile hay or straw infusion may be added. The amoebae grow in the water of condensation or on the more solid substance, from which they can be picked out and transplanted until "pure mixed cultures" result. In general a medium should be employed on which bacteria do not grow rapidly. Casagrandi and Barbagallo, in 1898, found that *Fucus crispus*, 5 per cent strong, when made distinctly alkaline, keeps bacteria down and gives a good medium for many kinds of amoebae. They found that *Entamoeba coli* and *E. blattae*, however, would not grow on such media, and came to the conclusion that "only free-living amoebae having a contractile vacuole" can be grown in artificial cultures. Frosch, in 1898, cultivated earth amoebae (limax type) on a variety of media, the most satisfactory consisting of ½ gram agar, 10 grams alkaline bouillon, and 90 grams water. Tsujitani (1898) made successful cultures on a medium consisting of 1 to 1.5 grams agar, 20 grams nutrient bouillon, and 80 grams water. This was filtered, made alkaline, and sterilized.

The results of these earlier workers showed in general that a number of artificial nutrient media may be suitable for the cultivation of amoebae; that a certain alkaline reaction is necessary; and, apparently, that bacteria are absolutely necessary. The latter conclusion, however, was weakened by the observation of Tsujitani, who found, in 1898, that one species of amoeba would grow on the dead bodies of one species of bacteria.

Vahlkampf, somewhat later, pointed out that the number and variety of media on which amoebae would grow are practically unlimited, and that too much stress is often laid upon the exact composition, and even upon the alkalinity, an acid reaction, in some cases giving satisfactory results. He used a number of media, both fluid and solid, getting favorable results with all in connection with his excellent studies on *Vahlkampfia* (*Amoeba*) *limax*, the first of the

free living limax types to be carefully and accurately studied. He used as solid media the following combinations:

1. Heyden Nahrstoff, 1 to 2 grams; agar, 1.5 grams; tap water, 100 grams.
2. Somatose, 1 to 2 grams; agar, 1.5 grams; tap water, 100 grams.
3. Nutrose, 1 to 2 grams; agar, 1.5 grams; tap water, 100 grams.
4. Witte's peptone, 1 to 2 grams; agar, 1.5 grams; tap water, 100 grams.
5. Agar, 1.5 grams; tap water, 100 grams.
6. Fucus crispus, 5 grams; tap water, 100 grams.

The bacteria used by Vahlkampf were *Bac. subtilis*, *alvei*, *tumescens*, and *B. asterosperus*. The best results were obtained by seeding in shallow Petri dishes which permit of daily microscopical examination.

The standard present-day agar-method of making pure mixed cultures was successfully used by Musgrave and Clegg (1904), and is now generally employed. The medium is made up as follows:

Agar, 20 grams; Witte's peptone, 1 gram; Liebig's beef extract, 0.1 gram; sodium chloride, 1 gram; distilled water, 1,000 grams.

These are dissolved by boiling or by autoclaving, and then made 1 to 1.5 per cent alkaline by titration to phenolthalein, using sodium hydrate. This is cleared with the whites of two eggs and filtered. The filtrate is sterilized and tubed, and is ready for use either as slants or in Petri dishes. The surface is streaked with the material containing the desired amoeba and left in room temperature.

In place of agar, some observers find albumen water an excellent medium. Behla, in 1898, described some early work by Balsamo Crivelli and Maggi, who cultivated an amoeba (which they called *A. albuminis*) on a nutrient medium of albumen, with or without the addition of weak carbolic acid. He further quotes Rina Monti, who used a similar medium consisting of a solution of albumen in distilled water, two parts albumen to one of water acidified by carbolic acid. Quite recently Gläser has had excellent results with free living amoebae by using a few drops of albumen (2 to 3) in a 6 cm watch crystal of tap water into which a piece of agar with amoebae is dropped. Enormous quantities of amoebae were obtained in three days at room temperature. Gläser does not recommend this for pure culture work, but, for cover glass smears with thousands of amoebae, he regards it as superior to solid media cultures.

A number of limax types, capable of living on agar, pass into a flagellated stage. Such forms have been described by Wasielewsky and Hirschfeld in 1910, by Whitmore in 1911, and by Alexeieff in 1912. The former used an albumen medium and Whitmore the alkaline agar method of Musgrave and Clegg; the latter finding that flagellated stages of his *Trimastigamoeba philippinensis* could be raised from the ordinary cysts and vegetative forms by flooding his

agar plates with a few cubic centimeters of tap water, the swimming forms appearing in about 2 hours, becoming very numerous in 4 hours, and returning to the amoeboid phase after 20 hours.

Although "pure mixed cultures" are perfectly satisfactory for the ordinary amoeba culture, the question arises: Can pure cultures in a bacteriological sense be made and continued in transplant generations? A number of *a priori* arguments have been raised against the possibility of this result. Vahlkampf expresses these objections very clearly, pointing out that amoebae—typical animals—can not live on dissolved proteids and salts in the surrounding medium, but must take their food in the complex form of proteids. He concludes that it would be impossible to get pure cultures or to raise them without their natural food-bacteria. On similar *a priori* grounds an answer to this would be that living proteid food is not necessary to supply the needs of animals, and, if dead organisms or parts of organisms could be engulfed and digested, pure cultures, in the sense of only one strain of living things, would result. Tsujitani, for example, has already been referred to as having cultivated one strain of amoeba on one species of bacteria used when dead. He does not mention transplants nor continued culture generations. This work was repeated and confirmed by J. T. Chase and A. W. Williams (see Williams, 1911), who succeeded in growing one strain of amoeba through 10 culture generations on agar cultures of dysentery bacilli killed by heating. Still more interesting is Williams's work with sterile extracted animal tissues rendered bacteria-free by special precautionary methods. Tissues of brain, liver, kidney, and other organs were placed on agar in a thermostat at 36° C for 24 hours; small quantities of the broken-up tissues were then mixed with the amoebae on agar plates. Usually in abundant growth or pure culture resulted in 24 hours at 36° C., or in from three to five days, at room temperature. In this way, Williams has cultivated *Entamoeba coli* (Musgrave and Clegg's strain 11524), *Entamoeba intestinalis*, *E. cobayae*, the first through 54 culture generations, the second through 30 generations, and the third through 15 generations, at 36° C. up to the time her paper was written. The question of pure cultures, therefore, in the light of her carefully guarded experiments seems to be well beyond the reach of adverse *a priori* criticism.

The probability of cultivating pernicious forms of Entamoeba on artificial media is well established by Williams's results, and it bids fair to be only a matter of time before *E. histolytica* and *E. tetragena* will be raised in sufficient quantities for detailed study of all phases of their life history.

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THE RELATION OF ANAPHYLAXIS TO IMMUNITY AND DISEASE.

By Dr. VICTOR C. VAUGHAN, University of Michigan, Ann Arbor, Mich.

INTRODUCTION.

Studies of the phenomena of protein sensitization, so-called anaphylaxis, have given us quite a new idea of many of the problems of immunity and disease. The only way in which cells of any kind—bacterial, protozoal, or animal—can grow and multiply is by elaborating ferments which split up the pabulum within their reach, thus preparing a food supply. The cell which can no longer supply a digestive ferment is already dead, whatever be the kind or amount of pabulum surrounding it. The cell which supplies only such ferments as can not digest the food supply within its reach dies immediately. This is the fundamental fact of the general immunity possessed by higher animals against the lower forms of life. As was shown in my laboratory some years ago, there is no constant and fixed relation between the toxicogenic and pathogenic properties of bacilli. The bacillus prodigiosus contains enough intracellular poison to kill guinea pigs when injected intraperitoneally in doses of 1:90,000 body weight, while the anthrax bacillus requires 1:1,700, and still the former is nonpathogenic and the latter highly pathogenic. The explanation lies in the fact that the prodigiosus can not grow and multiply in the animal body because its secretions do not digest the proteins of the animal body, or, what is more probable, the secretions of the body cells destroy the bacillus. On the other hand, the anthrax bacillus elaborates ferments which do digest the proteins of the animal body, while the body cells do not destroy the bacillus, and thus serve the microorganism with food. For these same reasons a given bacillus may be pathogenic to one species or to one race and wholly devoid of effect on other animals. Furthermore, the virulence of different strains of the same microorganism varies with the abundance and the strength of the digestive ferment. One strain of the pneumococcus may not kill guinea pigs in less doses than 1 cubic centimeter of a 24-hour culture, while another may kill in one-millionth of this amount, and still when animals inoculated with the

two strains are dead the same number of bacilli or the same amount of bacillary cell substance will be found in both. One strain has multiplied a million times faster than the other because of the greater abundance and effectiveness of the secretions which enable it to grow.

The great lesson which we have learned from our studies of anaphylaxis is that the digestive secretions of body cells may be developed and modified by the kind of protein brought into contact with them. When a foreign protein is introduced into the animal body certain cells develop a specific digestive ferment which splits up that protein and no other. Cellular digestion is a physiologic process and it is normally specific inasmuch as the secretion of each kind of cell splits up the pabulum in such a way as to supply the needs of its own cell, but the pabulum upon which the cells of the body normally feed consists of the proteins of the blood and lymph. From these sources all the cells of the body select their food material through the agency of their digestive ferments. Normally there is much preparation of the foods upon which the cells of the animal body feed. The proteins taken into the alimentary canal are broken up by the digestive juices into amino acids, and in this process they lose all their distinctive character. During absorption or soon thereafter the amino acids are put together again, but now so grouped as to form the proteins peculiar to the species. From the special proteins thus prepared each kind of body cell obtains its nutriment. Parenteral digestion is a physiologic process in which the material acted upon, the cleavage agents, and the assimilating cells are constant. However, even with all this preparation of food for the body cells it must happen at times that foreign proteins, as such, find their way into the blood and lymph. In order to digest this unusual pabulum the body cells elaborate a specific ferment, which digests this protein and no other. This is one of the fundamental and central facts of protein sensitization.

The second fundamental fact in protein sensitization is that every protein molecule contains a poisonous group. This is true of all bacterial, vegetable, and animal proteins, so far as they have been investigated. The poisonous group in the protein molecule is the same so far as its physiological action is concerned, whatever be the nature of the entire molecule of which it is a part. Chemically there must be differences in the poisonous groups of different protein molecules, but, as has been stated, in physiological action one can not be distinguished from another. It may be that more exact studies will show slight variations in physiological effect. I have designated the poisonous as the primary group in the protein molecule. I have also suggested that it be regarded as the "archon" or keystone of the

protein molecule. It probably contains the benzol ring with nitrogenous side chains. Attached to this primary group are secondary groups which may be designated as the "characteristic" groups, because it is in these that one protein differs from another. The sensitizing properties of proteins reside in the secondary groups, because it has been shown that these, when freed from the poisonous group, may sensitize animals to the unbroken molecule. It is for this reason that the special ferments elaborated in the cells of the animal under the influence of a foreign protein are specific. The poisonous group, when detached from its secondary or characteristic groups, does not sensitize either to itself or to the whole protein from which it came. In the original protein molecule the poisonous group is rendered inert physiologically by being combined with the secondary groups. In its free state it becomes a poison on account of the avidity with which it disrupts other protein molecules and combines with their secondary groups. The protein molecule may be compared to a basic or neutral salt, and it becomes more and more poisonous as its basic elements are removed, and when the free acid only is left its maximum toxic action is reached. The protein poison is a powerful agent. In the purest form in which I have been able to obtain it, and this probably is far from chemical purity, it kills guinea pigs of from 200 to 300 grams weight, when injected intracardiacally in doses of 0.5 milligram. When used intra-abdominally this dose must be multiplied by 16, and when given subcutaneously by about 32. These differences in effect, according to the method of administration, are of importance and are accounted for by the fact that the poison attacks and is neutralized by the body proteins with which it first comes in contact.

Whenever neutral proteins undergo cleavage as the result of the activity of proteolytic enzymes there are steps in the process when the activity of the poisonous group is made more manifest, and this proceeds as the basic elements are stripped off. In this way the poison is in part liberated in alimentary digestion. Biedl and Kraus have shown that the action of the anaphylactic poison and that of pepton are identical. This is necessarily true because the active group in both is the same. The protein poison is set free or activated by the alimentary proteolytic enzymes, and, if it were a readily diffusible substance, all proteins would be poisonous to man when taken by the mouth. But since it does not speedily pass through the alimentary walls and since further cleavage renders it inert we escape its poisonous action. In parenteral digestion of proteins there are no walls to prevent the diffusion of the poison, and consequently more or less injury always results.

Anaphylactic shock is such a striking phenomenon that for a long time it obscured the essential facts of protein sensitization and led

investigators far astray. When compared with immunity, the two seemed antipodal. In one the life of the animal is saved; in the other it is jeopardized, and, in the majority of instances, lost. Indeed, it was a misconception which led Richet to select the term "anaphylaxis." I still hold to the following statements concerning protein sensitization first formulated by Wheeler and myself:[1]

(1) Sensitization consists in developing in the animal a specific proteolytic ferment which acts upon the protein that brings it into existence and on no other.

(2) This specific proteolytic ferment stored up in the cells of the animal as a result of the first treatment with the protein remains as a zymogen until activated by a second injection of the same protein.

(3) Our conception of the development of a specific zymogen supposes a rearrangement of the atomic groups of the protein molecules of certain cells in the animal body or an alteration of the molecular structure. In other words, we regard the production of the specific zymogen not as the formation of a new body, but as resulting from an alteration in the atomic arrangement within the protein molecule and a consequent change in its chemism.

(4) Some proteins in developing the specific zymogen produce profound and lasting changes in molecular structure, while the alterations induced by others are slighter and of temporary duration, the molecular structure soon returning to its original condition.

(5) Bacteria and protozoa are living, labile proteins, while egg white, casein, serum albumin, etc., are stable proteins. The proteins of the one group are in an active and those of the other in a resting state, but both are essentially proteins, made up of an acid or poisonous chemical nucleus and a basic or nonpoisonous group. The former in its effects upon animals is the same whether derived from the living or the dead protein, and the latter in the one instance induces specific immunity and in the other specific susceptibility; but the immunity and susceptibility each consists in developing in the animal body the capability of splitting up a specific protein. If the living protein be split up before it has time to multiply sufficiently to furnish a fatal quantity of the poison, the animal lives and we say that it has been immunized. If the stabile protein be introduced into the animal, it leads to the development of a specific proteolytic ferment, and if enough of it to supply a fatal dose be reinjected after this function has been developed the animal dies. The first or sensitizing dose of egg white injected into an animal is digested just as surely as is the second, but the process goes on so slowly that we see no effect; but in fact the first dose has affected the animal profoundly, so profoundly that the change wrought in certain cells of the animal body persist for months, possibly for years, and may

be transmitted from the mother to her offspring. We do not say that the animal is sensitized unless some immediate and striking effect follows our treatment, but this is wrong. An immediate effect, especially a fatal issue, on reinjection depends upon the rapidity with which the protein is split up and its poisonous constituent set free. The sensitizing injection leads to the development of a specific enzyme, and the protein of this injection is so slowly digested that the poison set free at any one time is not sufficient to produce any recognizable effect. If time enough be allowed between the sensitizing and the reinjection for the accumulation of a large amount of the specific enzyme, then the protein is split up promptly and anaphylactic shock and death result. These views concerning protein sensitization, first offered in 1907, have been on the whole confirmed by later investigators, generally without credit to those who originally proposed them.

The fact that an animal is sensitized before the time when a reinjection is followed by anaphylactic shock has been conclusively demonstrated by inducing passive anaphylaxis with serum taken from animals in the so-called preanaphylactic state. Likewise it has been shown that serum taken from animals in the so-called anti-anaphylactic state passively sensitizes fresh animals.

THE PREVENTION OF ANAPHYLACTIC SHOCK.

From a practical standpoint anaphylactic shock is the least important of the phenomena of sensitization. It is always an artificially induced condition, and the only importance it brings to the practitioner is that he should know how to prevent it in serum therapy. Although the procedure necessary to protect the patient against anaphylactic shock was first pointed out by Vaughan, jr., the best work along this line has been done by Besredka. The last-mentioned investigator has shown that the intraperitoneal injection of from one-fiftieth to one one-hundredth cubic centimeter of the serum in sensitized guinea pigs renders them so positively refractory that five hours later intracerebral injections are wholly without effect. Besredka has made quite a thorough study of the means by which anaphylactic shock in serum therapy may be averted, and he states his conclusions as follows:

(1) Preparatory heating of therapeutic sera to 56° tends to suppress the phenomena of sensitization without wholly averting them. Besredka states that all therapeutic sera prepared at the Pasteur Institute are subjected to this temperature, and that instances of anaphylactic shock are less frequent, and, when seen, less severe in France than in countries in which this preliminary heating is not practised.

(2) Alcoholic and ether narcosis give a complete, but transitory, immunity to anaphylactic shock. (This is not practical.)

(3) Preventive injections of serum heated to 80° produce a certain and lasting immunity, but it develops slowly and is accompanied by slight reaction. (It will be understood that only that portion of the serum used to prevent anaphylactic shock is heated to this temperature, which would render antitoxin inert.)

(4) The best method of averting anaphylactic shock is either by rectal injection of the unheated serum, or, better still, by the subcutaneous injection of a very small dose.

The recommendation of Vaughan, jr., is that in all cases in which anaphylactic shock may be feared a preliminary injection of from 0.1 to 0.2 cubic centimeters should be made, and after an interval of two hours, provided no untoward symptoms have appeared, the full dose may be given. The suggestion is made by Rosenau and Anderson that all individuals who have shown any tendency to asthma, together with those who have received previous injections of the serum, with an interval of 12 days or longer, should be included among those in whom anaphylactic shock may be feared. It is not held that even with these precautions all the symptoms of serum disease will in all cases be averted, but serious anaphylactic shock is not likely to occur.

SERUM DISEASE.

The studies of v. Pirquet and Shick[3] on diseased conditions induced by therapeutic sera have proved of great value in explaining the phenomena of protein sensitization. In a certain per cent of individuals who receive injections of horse serum for the first time certain well-defined symptoms develop, usually from 6 to 12 days after the injection. The symptoms consist of fever, more or less general edema and rash, generally urticarial, though sometimes erythematous. The rash is usually accompanied by intense itching, and it may cover not only the entire surface of the body but extend to the visible mucous membrane of the mouth and throat, about the anus, and into the rectum. The lymph glands may be enlarged, and pain in the joints is often severe. The per cent of persons thus affected by the first dose of horse serum increases with the quantity of serum employed. The explanation offered by v. Pirquet is that some of the unchanged serum remains in the body until sensitization is sufficiently developed to "bring the effects of the toxic body up to the level of clinical observation." This demonstrates that a reinjection is not necessary in order to develop the state of protein sensitization. The evolution of the specific enzyme begins soon after the introduction of the foreign protein and gradually proceeds, and the liberation of the protein poison increases parri passu. It is not until

the effects of the liberated poison approach the "level of clinical observation" that we recognize them, but this is not at the beginning of the process. Sensitization of the body cell probably begins as soon as the foreign protein comes in contact with it. The foreign protein so impresses the body cell that the latter undergoes such changes in its intramolecular structure that it elaborates a new and specific enzyme. The fact that soluble proteins sensitize so much more promptly and efficiently than suspensions renders it probable that cellular penetration is essential to the most thorough effect. The additional fact that relatively dilute solutions sensitize more promptly and more efficiently than more concentrated ones suggest that degree of molecular concentration has some influence upon the processes of sensitization.

Von Pirquet and Shick observed two kinds of reaction in those who received reinjections after intervals of 12 days or longer. In some the reaction is of the same character as that described above, but it appears two or three days earlier. It is supposed that those in whom this form, designated as "accelerated reaction," occurs have partially passed beyond the condition of sensitization, but easily resume it on receiving the reinjection. There seems to be no danger to life in either the "delayed" or "accelerated reaction." The one accompanied by marked danger to life is the "immediate." In this the effects manifest themselves within a few hours, often within a few minutes after the reinjection. These individuals are in a fully sensitized condition, and it is in these that anaphylactic shock should be feared.

There are instances in which the first injection of horse serum has induced alarming, and rarely fatal, anaphylactic shock. These have been reported with sufficient frequency to cause more or less anxiety in the employment of therapeutic sera; besides, it raises the very important question as to why a small per cent of persons should be, apparently naturally, susceptible to an agent to which the great majority are immune. Cases of "horse asthma," in which more or less violent symptoms, such as sneezing, inflammation of the conjunctiva and the mucous membrane of the upper air passages, result from riding behind horses, are well known. The flying hairs from horses carrying minute quantities of protein are inhaled and may cause local sensitization, and it may be that this accounts for the instances of anaphylactic shock observed after first injections of horse serum.

VACCINATION.

The valuable research of v. Pirquet[3] on vaccinia has done much to elucidate the problems of sensitization. We quote the following from one of his later communications on this subject:[4]

"The first vaccination in healthy children shows an extremely constant symptom complex. Some minutes after the vaccination, a traumatic reaction, in the form of a very slight redness, appears, which lasts about one day, and leaves a small scab surrounded by normal skin. On the third or fourth day a small red papule appears, which indicates the beginning of the specific reaction. Between the fourth and sixth days, the middle portion of the papule becomes more elevated (papilla formation), the outer part becomes flat and forms a small red circle then the 'aula' around the papilla. From now on the papilla increases in size quite regularly, about one millimeter a day, and the solid papule is transformed into a blister. The aula remains of the same size and is protruded only by the extension of the papilla. Between the eighth and eleventh days the aula increases to a large, slightly elevated plaque and 'area.' The papilla ceases to grow and becomes yellow. Between the eleventh and fifteenth days the area reaches its highest development and then disappears slowly, whereas the papilla dries and a large scab falls off, leaving a scar." * When daily vaccinations on the same person are made for a fortnight the papilla appear in order corresponding to the day of vaccination, and the inflammation of the area appears on all the vaccination points simultaneously. "Although the vaccinations were made on successive days, the area develops around all the vaccination points at the same time; that is, at the time when its development is due on the first vaccination points. From now on the papilla of the later vaccinations stop growing, as does the papilla of the first vaccination. In those vaccinations which have been made from this time on, the state of papilla formation is no longer reached. Another type of reaction occurs—"early reaction." In this reaction a papilla is formed, reaching its development in 24 hours and from then on gradually disappearing.

The above nicely explains not only the development of vaccinia and the way in which it protects against smallpox, but also vaccination in other infectious diseases. The avirulent organism of vaccinia still has the protein constitution of the virulent one of smallpox. It has been modified in function, but not seriously altered in essence by its passage through the cow. The proteins constituting its molecules have not been changed, or, if at all, so slightly altered that one form still sensitizes to the other. The modified virus sensitizes the body cells and by this we mean that it causes the cell to elaborate a specific enzyme that digests and destroys the virus. The body cells retain this new function and when the smallpox virus finds its way into the body it is digested and destroyed before it has time to multiply sufficiently to cause disease. This is the basis of all bacterial and protozoal vaccination. In securing his vaccine for chicken cholera Pasteur modified the organism by successive growths on artificial culture media. That for anthrax he obtained by growth at relatively high temperature and that for rabies by drying the cord. The vaccine for typhoid fever is obtained by the use of cultures killed by heat. All of these processes in the special instances modify the proteins of the organisms so slightly that they still sensitize to themselves. This is protein sensitization and gives protein immunity. It is wholly different from toxin action and toxin immunity, and we should not confuse the two by discussing one in terms

of the other. In protein immunity there is no antigen and no antibody, and we will proceed more understandingly if we stop employing these terms in discussing protein sensitization. The toxins are either ferments or closely related bodies, and the substance that digests the protein on reinjection or in the sensitized state of the animal is a ferment and it is proper to speak of it as consisting of amboceptor and complement, but further than this the nomenclature introduced by the genius of Ehrlich to explain toxin action and reaction has no place in the literature of sensitization.

If what has been stated be true, protein sensitization is a most important factor in acquired immunity, and it will be well to discuss methods of using so powerful an agent in combatting disease. It should always be held in mind that any protein contains a powerful poison, and that no unbroken protein can be injected into the body without carrying with it this poison, and moreover, the parenteral digestion of a protein means that its poisonous group will be set free or activated in the body. The liberation of this poison occurs, not in the alimentary canal, the walls of which may protect the body or from which it may be rejected by vomiting or purging, or by both, but in the blood and tissue, and there is no escaping its effects. It is a poison, not a toxin, and there is up to the present time no known antidote for it. The indiscriminate employment of protein injections now being made should be most positively condemned.

Work done in our own laboratory indicates that with some proteins at least the sensitizing and poisonous groups may be separated, and that when this is done the former sensitizes quite as efficiently and sometimes much better than the unbroken protein containing its poisonous group. In animals the nonpoisonous part of the typhoid protein gives immunity to the living bacillus to a much greater degree and more promptly than the unbroken bacillus, either alive or dead. It is freely soluble and the more soluble protein sensitizers are the more promptly and efficiently do they act. But the old idea that in order to protect a man against disease you must make him sick—and the sicker you make him the greater the protection you give him—is so strong in the profession that no one will listen to the use of a nonpoisonous split product to protect one against typhoid fever.

That the tuberculous animal behaves quite differently from the nontuberculous on receiving injections of the tuberculin protein, whether it be in the form of the living bacillus, in dead cells, or in solution, has been abundantly demonstrated. Before Koch gave us tuberculin, Arloing and Courmont had come to the conclusion that the tubercle bacillus produces soluble substances which reduce the natural resistance of the body and render it more susceptible to reinfection. This corresponds closely with the first impression made by observation of the phenomena of anaphylaxis, the impression that

led Richet to select this term. In 1891 Koch described a perfect example of protein sensitization as we understand it to-day. He stated that when a healthy guinea pig is inoculated with the living tubercle bacillus there is no change at the site of inoculation until from 10 to 14 days later, when a hard lump forms, finally opens and ulcerates, and continues until the animal dies. On the other hand, when a tuberculous guinea pig is inoculated with the living bacillus, on the second or third day a lump forms, soon becomes necrotic, falls out, ulcerates for a time, and finally heals without any infection of the neighboring lymph glands. In 1897 Trudeau observed that when healthy rabbits receive injections of virulent cultures in the eye, there is little to be seen for about 14 days, when with increasing vascularity tubercles form in the iris after which inflammation extends and the eye is practically destroyed within from 6 to 8 weeks. Like treatment of tuberculous rabbits develops an iritis within from 2 to 5 days, but at the end of the second or third week at a time when the controls begin to develop destructive changes, the inflammation begins to subside. Later studies have confirmed and amplified these, and it has been found that death may be induced within 24 hours by injecting a large amount of a living culture into a tuberculous animal.

The same difference between healthy and tuberculous animals has been observed in their response to injections of dead cultures of the tubercle bacillus. The first observation along this line, so far as we know, was made by Strauss and Gamaleia, who found that when large numbers of dead tubercle bacilli are injected into tuberculous animals death results while similar amounts are without immediate effect upon healthy animals.

When we come to tuberculin, every phase of its action or its failure to act is explainable on the ground that the tuberculous animal is a sensitized one. Koch found that 0.5 gram of his preparation killed tuberculous guinea pigs, and induced no symptoms in healthy ones. A fraction of 1 milligram may cause marked symptoms in a tuberculous man, while many times this amount is borne easily by a healthy man. The inflammatory reaction about local tubercular lesions caused by injections of tuberculin is explained by the fact of the high degree of sensitization in their localities, and the cleavage of the bacilli. The ophthalmic, cutaneous, subcutaneous, and intravenous tests with tuberculin are all typical sensitization reactions. Even in the failure to respond to tuberculin seen in advanced tuberculosis we have the condition known as anti-anaphylaxis, which simply means that the anaphylactic ferment is exhausted by the large amount of material supplied by the bacilli in the body.

There is another line of evidence that in tuberculosis there is a condition of specific protein sensitization. This is to be found in

the fact that this disease is much more deadly in lands and among people who have recently come under its influence than it is where it has prevailed for many generations. In other words, the widespread and long-continued existence of the disease, slowly, and at the cost of much sickness and many deaths, brings a certain degree of immunity. The readiness with which the North American Indian has succumbed to this disease is a striking illustration, and Calmette has recently collected additional evidence on this point. He states that tuberculosis is being widely disseminated among peoples who have until recently been free from it. The world-wide wanderings of the white man are carrying the disease to every people, from the Laplander and Esquimaux of the arctics to the negroes and Malays of the tropics. Iceland, the Faro Islands, and the steppes of Russia are being infected and in these new regions tuberculosis exists in its most speedily fatal forms. The same author points out that recently discovered methods for the recognition of this disease even in latent states shows that among Europeans not more than 7 or 8 per cent reach more than 20 years of age without receiving the infection. Those who survive the first infection become more or less immune, and after that develop, when they do acquire the disease, the more chronic forms.

Römer[5] concludes that the less widely is tuberculosis distributed among a people, the greater is the case mortality, and, the wider the distribution, the smaller is the case mortality.

Still another fact of importance is that the most speedily fatal forms of tuberculosis, such as the miliary and meningeal, are much more frequent among children than among adults.

There is another matter of much importance in this connection which we must discuss. We have found the tubercle bacillus highly resistant to lytic agents, and it appears that its long experience as a parasite has led it to protect itself with layers of wax and deposits of fat, but proteolytic enzymes digest the most firm proteins. Friedberger has found that at least some strains of this bacillus are digested by the serum of healthy guinea pigs, and the researches of Merkl, Bail, and Kraus and his students have shown that tubercle baccilli placed in the peritoneal cavity of tuberculous animals respond to Pfeiffer's reaction. Some strains are dissolved in the peritoneum of healthy guinea pigs, but dissolution occurs more promptly and more completely in the peritoneum of a tuberculous animal. The healthy animal may have to depend upon its phagocytes to combat the invading bacillus, but the tuberculous animal supplies a specific proteolytic enzyme, and to this the fresh invader succumbs.

Nature is slowly immunizing the white man to tuberculosis, and the question arises whether or not the process employed by nature can be aided in any way. We think it can, and there is not before

the medical profession at this time a greater question than this, Is it possible to aid in eradicating tuberculosis by vaccination? What we need is a vaccine. Various methods of modifying the tubercle bacillus so that it could be used as a vaccine have been tried. The bovo-vaccine of von Behring was tried, but the increased resistance given by it was found to be of short duration. Attempts to reduce its virulence by age, heat, chemicals, and by submitting it to ultra-violet and other rays and emanations have been made. What we need is a tubercle protein sensitizer. It should be soluble and it should be free from the poisonous group in the protein molecule. In my opinion the nearest approach to this desired substance is the nonpoisonous portion of the tubercle protein, as prepared by the method of Vaughan and Wheeler. So far we have not been able to secure a uniform product. Some preparations seem to fill every requirement. They sensitize animals to the unbroken bacillus, dead or alive, and in surface tubercular lesions they cause inflammation about the tubercular area, and we have seen the tubercular tissue slough off and complete recovery result, but other preparations made from the same cellular substance by the same method seem inert. We have had similar difficulties with the sensitizing groups from other proteins. Some preparations from egg white sensitize to unbroken egg white, while others seem wholly without effect, and still all are prepared from the same material and in the same way. Evidently the sensitizing group in the protein molecule is a highly labile body and susceptible to influences which so far we have not been able to recognize. We have no difficulty in obtaining the poisonous group uniformly, but it is otherwise with the sensitizing body. Further work along this line is needed, and if an efficient and uniformly reliable sensitizer for the tubercular protein, free from the poisonous group, can be secured, all children should be vaccinated for tuberculosis, then, with protection against natural infection, the restriction of tuberculosis will be as completely under man's control as is that of smallpox. It should be clearly understood that the protection afforded by vaccination is relative and not absolute.

The studies inaugurated by Wright have demonstrated that vaccination is of service not only in prevention, but also in cure. Bacteria and protozoa are particulate, and in many diseases they are confined to limited localities. As we have seen, sensitization may also be local. No body cell is sensitized against a foreign protein until the latter comes in contact with the former, and penetration of the body cell is probably essential to the most efficient sensitization. The microorganisms of acne are located in the cutaneous tissue; and being particulate and not in solution, the area sensitized by them is small, if there be any sensitization at all. By vaccine therapy the

area of sensitization is greatly extended and the amount of lytic agent formed and made available is greatly increased. This being in solution and diffusible, digests and destroys the bacteria located in the skin. The same is true of the treatment of localized tuberculosis or of any other localized infectious disease. In vaccine therapy, as in vaccination, the great need is for soluble sensitizers free from poisonous content. When these are secured, and not until then, we may develop a vaccine therapy along scientific lines and expect to secure important results with it.

There is another possible way in which sensitization may be of service in treatment. We refer to the use of specific enzymes. This method is now being tried by J. W. Vaughan in the treatment of cancer. He sensitizes rabbits or sheep to the cancer cell by injections of finely ground cancerous tissue or the nonpoisonous portion of the same. When the large mononuclear leucocytes reach 25 per cent or more he bleeds the animal, lakes the blood with acetic acid, and collects the leucocytes in a centrifuge. These are rubbed with sterile sand in salt solution and passed through a Berkefeld filter. The filtrate contains the specific proteolytic ferment which splits up cancer cells. This is shown by incubating it with cancer cells when the poisonous portion of the protein molecule is set free, as is shown by the fact that when injected into fresh rabbits it causes sudden death. Incubated with other proteins the leucocytic extract liberates no poison. This leucocyte extract when injected in certain amounts directly into cancerous tissue induces anaphylactic shock. The effect of injections of small doses in parts of the body more or less remote from the cancerous tissue is now being tried, but it is too early to determine the value of this kind of treatment. This work seems to indicate that the specific anaphylactic enzyme for cancer cells is furnished by the large mononuclear leucocytes. It might be asked, Why not use the serum of the sensitized animal? This is not possible, for two reasons: (1) Repeated injections of the serum cause albuminuria, and (2) they sensitize to the proteins of the serum. When the leucocytic extract is filtered through a Berkefeld filter it does not sensitize to the blood protein; when this step in the process is omitted it does so sensitize. In work of this kind lies a promise of at least partially isolating the anaphylactic enzymes and studying their effects. It is not probable that this treatment will ever prove practical for the removal of large areas of diseased tissue.

FEVER.

It is interesting and instructive to read the older literature on fever in the light of the knowledge which has been gained in the study of sensitization. It has long been known that the parenteral introduction of proteins in small amounts, and especially repeated in-

troduction, leads to fever. The older literature on this subject, as well as an account of his own work, was given in 1883 by Roques.[6] In 1888 Gamaleia [7] showed quite clearly that fever accompanies and results from the parenteral digestion of bacterial proteins, and a year later Charrin and Ruffer [8] confirmed this work and extended it to nonbacterial proteins. In 1890 Buchner [9] produced the characteristic phenomena of inflammation—color, rubor, tumor, and dolor—by the subcutaneous injection of diverse bacterial proteins. In 1895 Krehl and Matthes [10] induced fever by the parenteral introduction of albumoses and peptons, but they did not obtain constant results, which we now know are secured only by regulation of the size and frequency of the dosage. In 1909 Vaughan, Wheeler, and Gidley [11] demonstrated that any desired form of fever—acute fatal, continued, intermittent, or remittent—can be induced in animals by regulating the size and frequency of the doses of foreign protein administered parenterally, and in 1911 Vaughan, Cumming, and Wright [12] extended the details of this work. These investigators established the following points:

(1) Large doses of unbroken protein administered intra-abdominally, subcutaneously, or intravenously, have no effect upon the temperature; at least, do not cause fever.

(2) Small doses, especially when repeated, cause fever, the forms of which may be varied at will by changing the size and the interval of dosage.

The following illustrations may be given: August 22, 1909, we injected the whites of three eggs into the abdominal cavity of a rabbit. The highest temperature of the fore period was 100.9°. After this injection the temperature was taken every two hours from 8 a. m. to 6 p. m., up to September 6. The animal was weighed each day, and its urine measured and tested for albumin. There was no fever; indeed, the morning temperature fell some days to 97°, and one day to 96.6°. The animal lost in weight slightly more than one-fifth of its original. The volume of urine averaged normal, and at no time did it contain albumin. On the other hand 0.05 cubic centimeters of egg white, filtered through cotton, injected intra-abdominally every half hour from 8 a. m. to 4 p. m. carried the temperature to 106.6°.

The intravenous injection of from 4 to 10 cubic centimeters of a dilution of egg white with an equal volume of salt solution every two hours from 8 a. m. to 6 p. m. had but little or no effect on the temperature, while the hourly injection of 1 cubic centimeter of the same solution and of much more dilute solutions carried the temperature within from 4 to 6 hours up to from 105° to 107°, and in some instances caused sudden death.

(3) The effect of protein injections on the temperature is more prompt and marked in sensitized than in fresh animals.

(4) The intravenous injection of laked blood corpuscles from either man or the rabbit causes in the latter, even in very small quantity, either in single or repeated doses, prompt and marked elevation of temperature.

(5) Laked corpuscles after removal of the stroma by filtration have a like effect.

(6) Protein fever can be continued for weeks by repeated injections, giving a curve which can not be distinguished from that of typhoid fever.

(7) Protein fever is accompanied by increased nitrogen elimination and gradual wasting.

(8) Protein fever covers practically all cases of clinical fever.

(9) Animals killed by experimentally induced fever may die at the height of the fever, but as a rule the temperature rapidly falls before death.

(10) Fever induced by repeated injections of bacterial proteins and ending in recovery is followed by immunity.

(11) The serum of animals in which protein fever has been induced digests the homologous protein in vitro.

(12) Fever results from the parenteral digestion of proteins.

(13) There are two kinds of parenteral proteolytic enzymes, one specific and the other nonspecific.

(14) The production of the nonspecific ferment is easily and quickly stimulated.

(15) The development of the specific ferment requires a longer time.

(16) Sensitization and immunity are different manifestations of the same process.

(17) Foreign, proteins, living or dead, formed or in solution, when introduced into the blood soon diffuse through the tissues and sensitize the cells. Different proteins have predilection places in which they are deposited and where they are, in large part at least, digested, thus giving rise to the characteristic symptoms and lesions of the different diseases.

(18) The subnormal temperature which may occur in the course of a fever or at its termination is due to the rapid liberation of the protein poison, which in small doses causes an elevation, and in larger doses a depression, of temperature.

(19) Fever per se must be regarded as a beneficent phenomenon inasmuch as it results from a process inaugurated by the body cells for the purpose of ridding the body of foreign substances.

(20) The evident sources of excessive heat production in fever are the following:

(*a*) That arising from the unusual activity of the cells supplying the enzyme.

(*b*) That arising from the cleavage of the foreign protein.

(*c*) That arising from the destructive reaction between the split products, from the foreign protein and proteins of the body.

In 1910 Friedberger [13] studied the effects of graduated doses of foreign proteins on the temperature of both normal and sensitized animals. With lambs' serum intravenously administered to normal guinea pigs he obtained the following results:

5.0 cubic centimeter equals fatal dose.
0.5 cubic centimeter equals limit for fall in temperature.
0.01 cubic centimeter equals upper constant.
0.005 cubic centimeter equals fever plane.
0.001 cubic centimeter equals lower constant.

In sensitized guinea pigs the above figures were changed to the following:

0.005 cubic centimeter equals fatal dose.
0.0005 cubic centimeter equals limit for fall.
0.00001 cubic centimeter equals upper constant.
0.000005 cubic centimeter equals limit for fever.
0.000001 cubic centimeter equals lower constant.

In 1911 Schittenhelm, Weichardt, and Hartmann [14] experimented with the effect of the parenteral administration of diverse proteins on animal temperature and came to the following conclusion, which, in our opinion, is well stated: "In severe experimental anaphylaxis there is a fall in temperature; in the lighter manifestations there is fever." We regard this as a confirmation of our conclusion reached some years earlier. "Small, especially repeated, doses of the protein poison cause fever, while large doses depress the temperature."

Some years ago Friedmann and Isaak [15] showed that after the parenteral introduction of foreign proteins the increase in nitrogen elimination is greater than can be accounted for by the protein injected. This has been confirmed by the work of Schittenhelm and Weichardt [16] and, as has been stated, Vaughan, Wheeler, and Gidley found the same in protein fever. Our explanation for the marked increase in nitrogen elimination has been given.

In intermittent and remittent fevers and in relapses in all infectious diseases the phenomena of protein sensitization are fully demonstrated. In the different forms of malaria, chill and fever correspond to the discharge of foreign protein into the blood just as promptly as anaphylactic symptoms follow the injection of the homologous protein in a sensitized animal. The moment the blood cells rupture and the protozoal protein is disseminated the sensitized cells discharge the lytic ferment by which the foreign protein is disrupted and destroyed, but in this process the poison is liberated.

Local sensitization is frequently established in the mucous membrane of the air passages and of the alimentary canal, also in the skin

for two reasons. In the first place, foreign proteins are frequently brought into direct contact with these tissues, and in the second place, as has been shown in my laboratory, foreign proteins introduced into the blood are frequently deposited in the skin and in the walls of the alimentary canal. These local sensitizations characterize many of the infectious diseases. The work of Dunbar and Weichardt on hay fever is a nice illustration. These investigators injected each other subcutaneously with minute quantities of pollen suspension. Immediately Dunbar, being a hay-fever subject, became dizzy and within a few minutes began to sneeze, then a whoopinglike cough began. The eyes were congested, and an abundant secretion flowed from the nose. The face became swollen and cyanotic, and soon the body was covered with an urticarial rash. After 24 hours these symptoms subsided. Weichardt, not being a hay-fever subject, was not affected. That this and kindred affections are not benefited by antisera was abundantly and positively demonstrated by the failure of the so-called hay-fever serum, which was found in no instance to be of special value, and in some it greatly intensified the symptoms.

Our common colds, or coryzas, are instances of local sensitization. Schittenhelm and Weichardt tell of a man who was so deeply sensitized by the inhalation of Witte's pepton that he could tell on entering the laboratory whether the pepton flask was open or closed, and some moist pepton painted on the skin caused the area covered to become red. The high degree of susceptibility to odors from the horse shown by some people has already been referred to. It seems in some instances that this susceptibility is transmitted from mother to child.

In conclusion, I wish to state that all the problems of protein sensitization have not been solved. It seems to be a physiologic law that the specific ferments elaborated by living cells are determined by the proteins brought into contact with them, but as yet we know but little concerning these bodies which we call ferments. That they are labile chemical bodies resulting from intramolecular rearrangement in the protein molecules of the cell seems a plausible theory, but, at present, it is only a theory. We know but little of the action of these so-called ferments upon their homologous proteins. Our knowledge of the chemistry of protein sensitizers is exceedingly limited, and, as I have pointed out, it is highly desirable that work in this direction should be prosecuted with vigor, because we need sensitizers free from the poisonous group. Furthermore, there is the question, why small doses of protein induce fever while large doses have no such effect. At present we have no satisfactory answer to this question. If it could be conclusively demonstrated that the toxins are ferments, the subject of the etiology of disease would be greatly simplified. I have elsewhere [17] given my reasons for holding that the toxins are fer-

ments, and in closing this paper I wish to formulate what I believe to be two biologic laws:

(1) When the body cells find themselves in contact with, or permeated by, foreign proteins, they elaborate specific ferments which digest and destroy the foreign proteins.

(2) When body cells are attacked by destructive ferments, they elaborate antiferments, the function of which is to neutralize the ferments and thus protect the cells.

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STUDIES ON THE LOCUS OF ANTIBODY FORMATION.

By FREDERICK P. GAY and G. Y. RUSK, from the Hearst Laboratory of Pathology and Bacteriology, University of California.

Since the critical work of Knorr [1] on toxins it has been generally accepted that antibodies are formed, not by a simple inversion of antigens, but by a reaction on the part of the cells of the animal that has received the antigen. Correlatively, it has been assumed that certain cells have a particular affinity for a given antigenic substance and are presumably specifically fitted to produce the corresponding antibody. Ehrlich's receptor hypothesis, while stating this assumption more concretely, has in no instance given direct proof that any particular type of cell gives rise to any given antibody. The experiment of Wassermann and Takaki [2] that demonstrated the apparent neutralization of tetanus toxin by brain substance is no longer regarded as a proof of the nerve-cell origin of tetanus antitoxin. Indeed the work of Loewi and Meyer [3] would show that injection of the toxin into nervous tissue produces an increased susceptibility of

the animal to tetanus toxin rather than an increased resistance. The fact that tetanus toxin disappears rapidly from the circulating blood of susceptible animals and may soon be demonstrated in the central nervous system would not, it would seem, prove conclusively that the toxin may not also have been fixed and neutralized by other body cells. At least it would seem necessary to assume that the cells responsible for the antitoxin formation must first fix the antigen. This proof of antigen fixation, indeed, constitutes one of the methods that have been employed in searching for the locus of antibody formation. The only other apparent method of determining antibody origin would seem to lie in the early demonstration of antibodies in given cell groups before they are demonstrable in the circulating blood.

Very little information, therefore, on the site of antibody formation has been gained from studies on toxin and antitoxin. Our information, inconclusive as it is, has been obtained from the work with other antibodies, and we would do well to consider first what data have been accumulated in respect to each of the antibody types in turn.

BACTERIOLYSINS.

Pfeiffer and Marx[4] inaugurated the first systematic attempts to discover the origin of lytic antibodies. Their work would seem to indicate very clearly that the protective antibodies directed against the cholera spirillum are elaborated in the leucopoietic organs, particularly in the spleen, but to a less extent in the bone marrow, inasmuch as extracts of these organs protect guinea pigs from infection before the blood serum does. Deutsch[5] essentially corroborated these findings with *B. typhosus* and Castellani[6] with *B. dysenteriae*. Levaditi's[7] conclusions from his work with the spirillum of hen septicemia were likewise corroborative, but his conclusions would not seem justified by the experimental evidence. These authors all agree that the spleen is not essential, as its removal at best but slightly inhibits antibody formation; the bone marrow and lymph nodes are secondarily concerned.

A careful inspection of Levaditi's experiments would seem to point to the blood stream as a possible source of antibodies, although his conclusions are different. Several authors, however, have attempted to disprove experimentally the local or leucocytic origin of the bacteriolysins. Thus Stenstrom[8] found that the injection of bacteria plus leucocytes led to less antibody production than the injection of bacteria alone. Pfeiffer and Marx found less antibodies in the ground leucocytes of immunized animals than in the plasma. Deutsch found the lysins were not present in peritoneal exudate and

Paetsch[9] extended this finding so as to include both pleural and peritoneal exudates and the lining endothelia of these cavities.

Viollé's[10] injections into the gall bladder for the rapid production of antibodies indicate the possible function of the liver in this connection, which is emphasized more distinctly in work with other antibodies.

HEMOLYSINS.

Metchnikoff[11] and Cantacuzène[12] originally suggested, on what would seem to be largely philosophical grounds, that the hemolysins may be formed by the leucocytes owing to the recognized phagocytosis of blood cells by the mononuclears. The output of "fixatives," according to Metchnikoff, varies directly with the degree of phagocytosis. There is direct evidence that goes to prove, however, that these bodies are not formed in the blood stream. McGowan[13] showed that no leucocytosis follows the injection of alien blood and Hektoen and Carlson[14] have shown by transfusion experiments that the antigenic properties of foreign blood cells disappear from the circulation within seven hours.

Among the fixed tissues, the liver and spleen seem to have shared the honors as the possible sites of hemolysin formation. Leuckhardt and Becht,[15] following the work of Hektoen and Carlson, found that the spleen alone of the organs in a dog that has received goat or rat corpuscles 24 hours previously has the property of immunizing new animals. As a proof of the temporary location of the red blood cells that have been injected, this evidence is undoubted, although well recognized from other work; as a proof of the spleen as the site of antibody formation it would seem to be negative. The statement by London[16] that splenectomy decreases the formation of hemolysins is categorically denied by Jakuschewitch.[17] Brezina[18] found that a specific serum against the leucopoietic organs had no effect in disturbing hemolysin formation. Carrel and Ingebristen[19] have produced hemolysins in the growing embryonic spleen.

The evidence in favor of the liver as the site of hemolysin formation is more positive. Both Cantacuzène[12] and McGowan[13] have shown the function of Küpfers cells in the destruction of red blood corpuscles. Muller,[20] in an interesting paper, has apparently traced normal hemolysin formation to the liver and has even been able to stimulate its excretion in the liver suspended in Ringer's solution outside the body, by transfusing it with solutions containing iodine (iodipin). A further contribution to the stimulating effect of iodin compounds is given by Hektoen[21] who was able to increase the output of hemolytic sensitizers in dogs by injecting sodium iodoxybenzoate. Viollés[10] method of producing antibodies by gall-bladder injection has already been referred to under bacteriolysins.

AGGLUTININS.

Whereas the evidence for bacteriolysin formation seemed to favor formation in the spleen or liver, the evidence for the locus of origin of the bacterial agglutinins points distinctly to the blood stream. Thus the work of Deutsch,[5] Castellani,[6] Rath,[22] Weil and Braun,[23] and Kraus and Schiffmann[24] all shows that the agglutinins appear in the blood serum before they are present in the extract of any organ. Although Gruber[25] originally suggested that the polymorphonuclears form the agglutinins, no experimental evidence goes to prove this. The experiments of Achard and Bensaud,[26] Widal and Sicard,[27] of Paetsch,[9] and of Kraus and Schiffmann[24] all seem to disprove leucocytic or local origin.

There is some evidence of agglutinin formation in the spleen offered by v. Emden,[28] Jatta,[29] and Girgoleff.[30]

PRECIPITINS (ANTIBODIES OF SOLUBLE ANTIGENS).

In the case of precipitin formation, again the evidence seems divided. It is shown by two sets of observers (Petit and Carlson,[31] Vaughan, Cumming, and McGlumphy[32]) that soluble antigenic substances like egg white or serum apparently disappear within a few hours from the circulating blood. This is shown by the impossibility of producing, in the one set of experiments, antibodies in another animal that is liberally transfused with such blood, and, on the other hand, by the failure to produce anaphylaxis in guinea pigs to the substance originally injected (egg white, Vaughan and collaborators). In apparent contradiction are the observations of several observers on the relation of leucocytosis to precipitin formation. Thus both Cantacuzène[33] and Swerew[34] have noted a marked hyperleucocytosis preceded by an absolute decrease in polymorphonuclears, which may reasonably be related to the liberation of precipitins. This observation fits in neatly with that of Hiss and Zinsser,[35] who obtained nonspecific bacterial precipitins from leucocytic extracts, and that of Stenstrom,[8] who found that hemologous leucocytes injected with the precipitinogen increases precipitin output. Kraus and Schiffmann[24] emphatically regard the blood as the source of precipitins, whereas Cantacuzène, in spite of his evidence in favor of the leucocytes, is inclined to trace precipitin formation to the spleen.

The liver is by no means to be overlooked in discussing precipitin formation. The work of Manwaring,[36] of Nolf,[37] and of Balizot,[38] on anaphylactic shock, would seem to point to the liver as the seat of action, and so, indirectly, owing to the relation that exists between anaphylaxis and precipitins, as a possible location of the latter substances.

It is evident from this brief survey of the literature that no general statement can be made on the locus of antibody formation in general. It may well be that each of the antibody types is produced in a different place or places. But even when we consider the possible seat of origin of any particular class of antibodies, we are struck by the apparent confusion in the acquired data. In the case of any of them we may still say that the antibody may be formed either in the blood stream or in the fixed tissues. There seems greatest agreement on the point that antibodies are formed either by the leucocytes or the leucocyte-forming organs. And yet a good deal of recent work points with increasing emphasis to the liver, an organ which, in view of its other functions, might logically likewise serve to produce antibodies.

Our own studies on antibody formation have been actively in progress for over a year. We regard them hitherto as largely preliminary and they have led rather toward establishing certain methods of attack and the evolution of working hypotheses of possible heuristic value than to any conclusion on the main subject at issue. Certain by-products of the investigation are in themselves of distinct interest, although their results are negative in so far as explaining antibody formation is concerned. Two incidental investigations may first be summarized before dealing with the work that bears more directly on the site of antibody formation:

I. THE EFFECT OF IODIPIN ON THE OUTPUT OF ARTIFICIAL HEMOLYSINS.[20]

Muller's[20] experiments led him to the conclusion that both normal sensitizer (amboceptor) and alexin are formed in the liver, but that their output depends on the stimulating action of the iodin of the thyroid gland. This author finds that the injection of thyroid preparations, or of various iodine preparations, notably of iodipin (Merck, 25 or 10 per cent of iodin), produces a distinct increase in from 24 to 36 hours of the normal hemolysins in rabbits and other animals. As already stated, this increase comprises not only an increase in alexin, as tested on blood cells sensitized by an artificial hemolysin, but an increase of the normal hemolytic sensitizer. Hektoen[21] has further found an increase in hemolytic sensitizers in dogs that received a single dose of goat's blood over the amount produced in control dogs on giving injections of sodium iodoxybenzoate. This alleged increase of normal hemolytic sensitizers immediately suggested the importance of determining the effect of iodin on artificial hemolysins, not only as a matter in itself of theoretical and perhaps of practical importance, but as bearing on the origin of antibody formation. Differences that might appear in the hemolytic potency of the sera of immunized animals would

presumably be more striking than corresponding differences in normal hemolysins, owing to the much greater strength of immune sera.

Our experiments deal, first, with the effect of a single injection of iodipin (Merck, 10 per cent) in rabbits that had been immunized by several injections of washed guinea-pig corpuscles. In several experiments a control animal that had been immunized in a similar manner, but that received no iodipin, was carried through. The animals with and without iodipin were bled before injection from the ear and at intervals subsequently; the separate sera were heated at once to 56° for one-half hour, and at the end of the experiment all were tested for hemolytic units at the same time with the same corpuscles and alexin. In other experiments a critical intravenous reinjection of the antigenic blood was given in two highly immunized rabbits, and on the following day one of them was given iodipin. Both sera were then tested at intervals for hemolytic potency. There was no evidence from any of these experiments that the injection of iodipin will increase the output of artificial hemolysins in the immunized rabbits.

II. HISTOLOGICAL STUDIES OF THE TISSUES IN IMMUNIZED ANIMALS WITH A COMPARISON OF CHEMICAL AND MICROCHEMICAL TESTS FOR GLYCOGEN.[40]

The histopathological studies of Gay and Southard[41] in serum anaphylaxis in the guinea pig have seemed an interesting contribution to the relation of structure to function. These authors found that anaphylactic intoxication is accompanied by definite lesions in the nature of hemorrhages and more particularly by fatty changes in parenchyma and in the endothelium. These endothelial fat changes could be produced in a few minutes following intravenous injection and obviously bear direct relation to the cyclonic symptoms of the syndrome. It occurred to us that similar evidence of functional cellular activity might be histologically demonstrable in the cells that are engaged in antibody formation. For this purpose rabbits were highly immunized by repeated intravenous injection of washed guinea-pig corpuscles and following a rest of two or more weeks were given a critical reinjection of 1 cubic centimeter of washed guinea-pig blood and at subsequent intervals bled and the tissues fixed in various ways and stained by many methods. The critical reinjection was aimed, obviously, to obtain the antibody-producing cells in a condition of highest activity.

In the first experiment a series of immunized rabbits received each the critical reinjection of antigen and were then bled at 1, 4, and 24 hours and 4 and 6 days subsequently. A careful histological study of tissues from this series showed in the 24-hour animal a very

marked increase of glycogen in the liver (Best's carmine stain, alcohol fixation). The animals bled before and after this period gave a regular increase and decrease of glycogen to the 24-hour maximum. A more careful control of this experiment has involved us in technical difficulties that seemed too time consuming and led, moreover, to far less encouraging results than the first experiment. The question of the effect of starvation on the amount of glycogen alone seemed unsurmountable; it was found, for example, that rabbits that have not been fed for two days have stomachs stuffed with food. We are still in doubt as to the significance of our first find of increased glycogen. An attempt to correlate the microchemical reaction of glycogen with a careful chemical analysis of total glycogen in the liver has, however, led to results of importance. So far as we are aware, there has been no systematic comparison between the chemical analysis of an organ and microchemical staining reactions in a sample of it. Dr. Rusk has studied the amount and distribution of glycogen in sections of 22 rabbit livers stained by the Ehrlich iodin method and the Best carmine method, with a chemical analysis of a greater (weighed) portion of the same livers, following Pflüger's method to the conversion of glycogen to glucose, and at this point introducing Betrand's modification of Fehling's method as more accurate in measuring the amount of copper reduced. It is found that the microchemical method serves to give somewhat definite information as to the amount of glycogen present, but within a limited range only, for when the chemical analysis showed very much or very little glycogen the staining method was at times wholly inadequate.

III. THE FATE OF HORSE SERUM INJECTED INTRAVENOUSLY IN NORMAL AND IMMUNIZED RABBITS.

The two general methods that have been and may be employed in seeking antibody origin are either to trace the course of the injected antigen to some group of cells or to seek the precocious appearance of antibodies in extracts of a given group of cells. The latter method is the one that has been used most frequently, but it is the former that we have employed. Our observations, some of which have already been published,[42] began with a study of the fate of horse serum injected into the blood stream of rabbits that had been immunized against horse serum. They have since led to further studies on the result of an initial injection of horse serum in normal rabbits. In all instances our results deal with an injection of one cubic centimeter of serum intravenously.

In beginning the experiments with immunized animals it was necessary first to determine the best method of detecting the antigen that

was reinjected. It was found that when horse serum is injected intravenously in rabbits that have a high precipitin content for horse serum it nevertheless remains demonstrable by the fixation reaction or the precipitin reaction for 24 hours. The reactions are carried out by adding the antigen-containing antiserum to a pure antiserum. After 48 hours the antigen is no longer demonstrable. The persistence of the antigen in the immune animal is accompanied by a fall in the precipitin value of serum (negative phase). It is of interest to note that although this antigen-containing antiserum will not precipitate or fix alexin spontaneously, it will react with another antigenic antiserum as well as with a pure antiserum. It was rather surprising to us to fail in any conclusive demonstration of the antigen by the fixation reaction in extracts of the organs of these same immunized animals (spleen, lymph nodes, liver, kidney, and muscles) either at the same time the antigen is present in the blood or even 24 hours later.

Of undoubtedly greater significance is the fact that neither the antigen-containing antiserum, nor the organ extracts of the same animal will sensitize guinea pigs to subsequent intoxication by horse serum. We compared the fixing values of pure horse serum and antigenic antiserum, and although one fixing dose of the horse serum will sensitize guinea pigs, many fixing doses of the antigenic antiserum fail to do so (at least 100). This would explain the results of Vaughan, Cumming, and McGlumphy[32] who found that egg white apparently disappears from the circulation in a few hours when tested for by the anaphylaxis reaction. It is perhaps also in harmony with the work of Hektoen and Carlson[14] and of Petit and Carlson[31] who proved by transfusion that the antibody-inciting factor in blood cells or in serum leaves the circulation in a few hours. We might possibly assume that the factor in the antigen that produces the antibody differs from the one that unites with it. (Cfr. Bang and Forsmann.[43]

The results of injecting horse serum into normal animals are also of interest. The horse serum is detectable by the precipitin and fixation reactions for several days. It apparently does not sensitize in large doses even after 24 hours. The fixation and precipitinogen antigen is present not only in the blood, but also in the various organ extracts (in this case carefully freed of blood) in uniform amounts on the seventh, eighth, ninth, and tenth day. Of greatest importance is the fact that the corresponding antibodies have begun to appear in the serum two or three days before the antigen disappears. Similar facts have been noted by Hintze.[44] It is evident then that not all the antigen is used up in producing the antibody. We have to imagine either that the antigen continues to unite with the cell or

stimulate the cell for some time after antibodies appear, or that the antibody stimulant differs from the antigen fraction that unites with the antibody. This latter hypothesis seems to us for the present the most valuable for a working basis. It explains, moreover, our own failure to produce anaphylaxis (cfr. also Vaughan and his collaborators), and also the results of Hektoen and Carlson. We are continuing our work with this as a working hypothesis and also with a possible further elucidation of the obscure phenomenon of anaphylaxis in mind.

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DISCUSSION.

Dr. W. H. PARK: Observations made on the injection of toxins and antigens into the blood or into the subcutaneous or other tissues indicate that for many antibodies several varieties of cells take part. The blood in an animal highly immunized to diphtheria toxin contains about 100 times the quantity of antitoxin as the tissue fluids. If toxin is added to antitoxin, union slowly takes place and the combined toxin is no longer able to excite the production of antitoxin. When a horse having a strongly antitoxic blood is injected intravenously with a definite amount of toxin very little production of antitoxin takes place, because most of it is neutralized by the antitoxin in the blood. The same amount injected in scattered spots subcutaneously will produce a large amount of antitoxin. The part absorbed into the blood would meet the same fate as that injected intravenously. It seems, therefore, certain that some or all of the cells in the area in the subcutaneous tissues that the toxin reaches must take part in producing antitoxin. If toxin is injected through the trachea into the lungs it acts in the same way as when injected subcutaneously. I have seen similar, though not as definite, results with the injection of various bacterial antigens. These facts seem to suggest that more varied cells than Dr. Gay indicates may take part in antibody formation.

Dr. VAUGHN thinks that the ferment is formed by different cells according to the sensitizer used. He referred to the work of J. W. Vaughan on sensitization to cancer proteins in which it appears that the ferment is formed in the large mononuclear leucocytes and that the sensitization is transitory. The fact that the nonpoisonous part sensitizes may be due to the presence of a minute trace of unbroken proteins. However, this seems highly improbable because this part does not sensitize to itself.

ON THE MECHANISM OF INTOXICATION IN PNEUMOCOCCUS ANAPHYLAXIS AND IN PNEUMOCOCCUS INFECTIONS.

Dr. E. C. Rosenow, of the Memorial Institute for Infectious Diseases, Chicago.

I wish to present here very briefly the results of experiments which it is believed throw some light upon the nature of intoxication in pneumococcus anaphylaxis and in pneumococcus infections. It is obviously impossible to give details or to discuss the various investigations which bear directly or indirectly upon results obtained. For these, reference must be made to the more complete papers published chiefly in the Journal of Infectious Diseases during the past few years.

When normal animals, guinea pigs and dogs, are injected intravenously with dead pneumococci or unautolysed extracts of pneumococci, they die in from 6 to 24 hours, depending upon the dose. Sensitized animals die at a relatively earlier period in both instances, and, in case of the extract, from typical symptoms of anaphylaxis.

When virulent pneumococci are suspended in NaCl solution, especially if ether is added; when unautolysed pneumococcus extracts or pneumococci are treated with immune serum, or with normal serum alone, or with a combination of these, there appears in solution, at a certain period, toxic material which kills guinea pigs and dogs with symptoms characteristic of anaphylaxis for each species. During the height of the toxicity for normal animals the mixtures containing the clear extracts have already lost a large part of their toxicity for the sensitized animals, and, finally, after longer residence at 37° C., the toxic action disappears both for normal and sensitized guinea pigs and dogs.

The toxic material obtained from pneumococci *in vitro* and in the sensitized animals does not differ essentially from that formed during pneumococcus infections, because the same type of toxic material is found in solution in various pneumococcus exudates, and because, after these are washed and again suspended, in NaCl solution at 37 ° C., more toxic material is formed *in vitro* and also, in an hour or more, following immediate injection into normal animals. When extracts of pneumococcus exudates are kept at 37° C. for a longer time, both the immediate and late toxic action disappears, just as in the case of the extracts, in NaCl solution, of artificially grown pneumococci. The pneumococci in the various mixtures which yield the toxic substance tend to become Gram negative and undergo disintegration. This is most marked in the extracts in NaCl solution. Only highly virulent pneumococci which contain an autolytic ferment, and which disintegrate rather rapidly, yield the highly toxic substance. Nonvirulent pneumococci and occasional virulent strains which either do not autolyse at all, or only very slowly, do not yield the toxic sub-

stance when suspended in NaCl solution. They do yield it, however, when treated with immune and then with normal serum, or with normal serum only; but, in each case, more slowly than highly virulent strains. The toxicity of the pneumococci disappears as they disintegrate and become Gram negative, and then no toxic substance can be obtained even when treated with fresh serum. The appearance and disappearance of the toxic substance, when virulent pneumococci are suspended in NaCl solution, has been proved to be associated with proteolysis. Proteolysis does not occur in case of nonvirulent pneumococci. When unautolysed, heated (60° C. one hour) pneumococcus extracts are treated side by side with sensitized and normal serum, it is found that the mixture in sensitive serum becomes toxic at an earlier period than that in normal serum, and it also disappears correspondingly earlier. Polariscopic measurements, made at the same time, show a more rapid decrease in levorotation in the former, indicating that here too the appearance and disappearance of the toxic substance occurs simultaneously with proteolysis.

By grinding pneumococci in the cold I have been able to show that little toxic material is preformed within them. The extracts obtained in this way, when injected at once, produce no immediate symptoms, but death within 24 hours; after they are kept at 37° C. for a time, they cause death in a few moments; and, still later, they produce neither immediate nor late symptoms. It seems certain, therefore, that mature pneumococci contain little preformed toxic matter, but yield a large amount as they disintegrate, both *in vitro* and *in vivo*, and it makes no essential difference whether they are grown artificially or in the infected host.

A comparative study of the toxicity of meat broth, and the corresponding clear culture, fluid or filtrate, shows that the latter is strikingly more toxic than the former. This has been shown not to be due to increase in acidity. Formol titration shows a corresponding increase in amino nitrogen. The exact source of the toxic material in this case is not entirely clear. I have pointed out that extracts of virulent pneumococci, in distinction to those of nonvirulent pneumococci, liberate a proteolytic enzyme. In order to determine whether this or other ferments obtainable from virulent pneumococci may produce similar toxic material from protein other than that contained in pneumococci, and at the same time produce protein cleavage, diminishing amounts of broth culture filtrates and filtered extracts in NaCl solution were added to meat broth and heated ascites meat broth, and placed at 37° C. It was found that both the broth culture filtrate and NaCl solution extract cause an increase in toxicity and amino nitrogen. Neither of these could possibly have had their origin in the small quantity of culture filtrates or extracts which were added. Hence a proteolytic enzyme escapes

from virulent pneumococci, which is responsible for part of the protein splitting, and the increase in toxicity when pneumocacci are cultivated in broth. A portion of the protein splitting, on the other hand, is intimately associated with the growth of the pneumococci. This is probably independent of the soluble ferment, because growth of nonvirulent pneumococci and streptococci, from which no soluble proteolytic enzyme can be obtained, causes both a splitting and an increase in toxicity when cultivated in broth.

The relation of protein splitting to the production of toxic substances is further shown by the following facts: The increase in toxicity in the mixtures of meat broth and culture filtrates and extracts is proportionate to the amount of protein splitting up to a certain point; after that, the toxicity diminishes and the splitting increases. In the broth cultures from which the pneumococci are not removed, whether killed by adding ether or not, the late diminution in toxicity is not observed. In this connection, the following interesting facts should be mentioned: The proteolytic enzyme is more resistant to heat and long standing in the broth culture filtrates than in the NaCl solution extracts. The toxic effect of clear pneumococcus extracts disappears promptly when heated to 60° C., whereas, in the NaCl solution suspensions, in which a rather large number of unautolysed pneumococci are still present, heating to 60° C., and even boiling for 10 minutes, often diminishes the toxicity only slightly. The toxicity now remains indefinitely on standing. This is especially true when the suspension is plunged at once into boiling water. In a similar manner the clear broth culture filtrates lose their toxicity more readily than the broth culture fluids from which the pneumococci are not removed, but not as readily as the clear extracts. Finally, when pneumococcus broth cultures, to which ether has been added, are kept at 37° C. for a long time and then filtered, and the proteolytic enzyme is no longer active, then heating the clear filtrate no longer diminishes the toxicity. From these facts, it appears that the toxic substance is really a stable compound, and that its disappearance from the mixtures is due to ferment action. Hence its disappearance on heating the clear extracts when the supply of material from which more toxic substance is made is limited, and its persistence in the suspensions when the supply is abundant.

Protein splitting is undoubtedly a factor in the production of the toxic substance; but that it is not the only factor is indicated by the fact that occasionally no perceptible increase in amino nitrogen is found in mixtures which are nontoxic at first, very toxic later, and again nontoxic still later.

From these facts it would appear then that there are three more or less independent sources of toxic material during pneumococcus infections, each one of which is closely related to protein cleavage.

They are (1) the pneumococci themselves (structural nitrogen); (2) growth in fluids or exudates (metabolic nitrogen); and (3) the action of the proteolytic enzyme on protein derivatives other than those from pneumococci. Certain facts indicate that other enzymes probably also play a rôle in the production and destruction of the toxic substances.

A study of the action of the toxic substances obtainable from pneumococci shows that the various drugs and procedures which protect sensitized guinea pigs against immediate anaphylaxis protect normal guinea pigs against the toxic substance. Injections in the jugular vein or right heart produce severer symptoms than injections in the left heart. Portal injections in well-fed guinea pigs produce little or no pulmonary symptoms; whereas, in starved animals, the symptoms are as marked as after jugular injections.

The toxic substance is soluble in ether. Guinea pigs which are injected a short time previously (2 to 24 hours) with nonfatal doses of toxic extracts, and especially of the extracts from which the toxicity has disappeared, are protected against fatal doses of extracts. This seems specific for pneumococcus products, because injections of NaCl solution, broth, and extracts of typhoid bacilli do not render guinea pigs refractory to toxic pneumococcus autolysates. After it was found that the toxic substance was soluble in ether, the protective effect of the extracts after ether extraction, and of the ether soluble portion, was tested. The former afforded protection, while the latter did not. It has been found further that the nontoxic extract affords protection in the guinea pig against properly gauged doses of virulent pneumococci, whereas the toxic substance hastens death.

Dead pneumococci and pneumococcus extracts, when injected in man, produce an increase in opsonin after an initial negative phase, while autolysed pneumococci, which have lost their toxic action, cause a more prompt rise in opsonin. By injecting proper doses of a combination of the toxic autolysates and autolysed pneumococci, I have been able to produce a continued negative phase similar to that observed in overwhelming pneumococcus infections. The mechanism of immunity seems paralyzed.

It is generally held that intoxication and immunization are due to the same cause. The above results indicate strongly, as also do certain clinical facts, that, in pneumococcus infections, at least, this seems not to be so, but that here there are produced substances which intoxicate, but which do not call forth protective reactions, and which probably actually interfere with antibody formation.

TRANSFER OF IMMUNITY THROUGH COLOSTRUM.

Dr. L. W. FAMULENER, Research Laboratory, Department of Health, New York City.

Over a century ago Hufeland[1] suggested that the milk excreted by a mother who had recovered from smallpox might exert a protective power over the nursing infant. He based this supposition upon the infrequency of smallpox among infants during the first months after birth. It is noteworthy that the theoretical explanation which he suggested took in account hypothetical antipoisons which roughly corresponded to our present idea of antitoxins or immune bodies.

Many years later the isolation and successful cultivation of specific organisms causing various infectious diseases was accomplished and methods of animal immunization were developed. Experimental studies showed, in some instances, that animals which had been previously immunized gave birth to young which were also immune to the specific infectious agent. This was commonly supposed to be an inherited immunity on the part of the offspring. In 1892 Ehrlich published his basic studies upon this subject. By those well-known experiments in which he immunized mice by feeding the toxalbumins, abrin and ricin, he showed that the young from such mothers were immune. He considered this a passive immunity and not a true inherited condition. The offspring in those cases acquired their antibodies in part before birth from the mothers' circulating fluids and in part after birth from the mothers' milk. He proved by placing normal young upon immune nurses that the milk transmitted specific antibodies which were absorbed unchanged by the nurslings and caused their immunization. Those studies firmly established the important rôle which the milk of immunized mothers may play in transmitting immunity to the offspring. It was soon found by Ehrlich and his coworkers that other animals, such as goats, when immunized against tetanus or diphtheria during the period of lactation excreted the respective antitoxins with the milk; the amount of antitoxins in the milk increased as the content in the animal's serum rose.

Since those early studies numerous investigations have been reported along similar lines, which show that the milk of highly immunized animals may contain any of the common types of antibodies; the presence of antitoxins, specific agglutinins, cytolysins, precipitins, etc., have been demonstrated in the milk of immunized animals. In some instances their transmission and absorption in an unchanged condition have been proved in the blood serum of the nursing young. We may accept as an established fact that antibody-bearing milk is an important factor, under certain restricted

conditions, in the transmission of immunity to the nursing young. This ability depends much upon the antibody concentration of the milk; the age of the recipient is also an important factor. In general, the newly born animal quite readily absorbs antibodies in an unchanged condition. As a general thing, animals actively immunized during the period of lactation do not show an antibody concentration of the milk, as compared to the blood serum, greater than one-twentieth of the serum value. The relative values are usually much less, probably depending in part upon the antigens used for immunizing purposes. Further, under such circumstances the increase in age of the offspring precludes the absorption of the antibody of the milk in an unchanged condition when taken as food.

Experimental evidence would indicate that the most favorable condition for the transmission of immunity from the mother to the offspring through the milk exists at the time of the birth of the young. This, naturally, means that the mother must be immunized some time previously in order that milk from the first may bear sufficient quantity of the specific substances. Since we have had an opportunity to carry out certain experiments along this line, a brief report of the results may prove to be of interest. Immunizations were carried out upon female goats, by repeated subcutaneous injections of washed sheep-blood cells, at different periods before the birth of the young. In order to prevent the young from taking the colostrum at birth before samples of their blood were secured, the adult's nipples were previously sealed with collodion. As soon as possible after the birth of the young, a blood sample was taken from the kid; then the seals were removed from the mother's nipples and a sample of colostrum taken; finally a blood sample was taken from the adult. Immediately after the first blood sample was drawn from the newly born animal and the colostrum sample taken from the mother, the young was permitted to suckle and remain with the mother from that time onward. Both blood and milk samples were taken from the mother and blood samples from the suckling at intervals for some time following the period of birth. The assembled samples, which had been kept in the ice box, were all tested at the same time in parallel, thus giving comparable results. In some instances the colostrum was found to contain more specific antibodies than the mother's serum did at time of birth of the young. Usually in those cases the immunization had been carried out several weeks previously, and the serum antibodies had greatly diminished in quantity. The antibody content of the colostrum milk rapidly diminished as the milk excretion set in and was usually negative after a few days. In case of twins, one was removed from the mother, a blood sample taken, and then placed upon cow's milk as a control. Samples of blood taken from kids at time of birth (before being

permitted to suckle mother) and those from the kid which was fed cow's milk never showed the presence of haemolysins by the test used. Therefore we must conclude that little, if any, passed from the mother-animal's circulation to the young before their birth. The kids which were permitted to suckle the immunized mother, thus getting the colostrum milk, showed considerable amount of the specific immune body in their blood serum on the first day following birth. Rarely did this content rise on the second day. Following this, the antibody content of the kids' blood gradually fell, similar to the ordinary passive immunity curve of the animal thus immunized.

If we are permitted to draw conclusions from this series of experiments, it becomes evident that the complex cytolytic antibody formed in response to blood-cell injections readily passes over (in an unchanged condition) to the blood of newly born suckling from the ingested colostrum of the previously immunized mother. But little, if any, passes over from the immunized mother's body fluids to the offspring before their birth. These experiments would indicate that the antibodies resulting from immunization of females before birth of the young tend to accumulate in the mammary glands and are excreted with the colostrum milk. The question arises, Do the natural antibodies likewise accumulate in the milk glands of normal mothers? If so, does the colostrum play a more or less important part by transmitting natural protective substances from the mother to the child? Is the transient resistance which infants commonly show against certain infections during the first weeks of life in part acquired in this way? Certain experimental evidence along these lines would lend support to such a supposition. This may partially account for some of the advantages which the breast-fed child enjoys over the bottle-fed infant in the struggle against disease.

[1] Cited by Neumann, Deutsche med. Wchnschr., 1895, 21 (part 2), p. 841.

ANAPHYLACTIC REACTION IN PELLAGRA PATIENTS, BY THE INOCULATION OF WATERY EXTRACT OF SPOILED MAIZE.

By Mr. GUIDO VOLPINO, charged with the course of bacteriology (with the collaboration of Drs. A. MARIANI, E. F. BORDONI, and L. ALPAGO NOVELLO).

1. The pellagra patients, when subjected to an inoculation of a certain quantity of watery extract of spoiled maize, either undercutaneous or into the muscular masses, which are insufficient to produce appreciable phenomena in the great majority of nonafflicted with pellagra, present after a few hours, very rare exceptions excluded, a, sometimes most accentuated, reaction of hypersensibility. Such a reaction manifest itself by dullness, drowsiness, and a state of semicoma,

or by a strong physical and nervous excitability. Such phenomena are accompanied in either case by a remarkable acceleration of the pulse, dyspnœa, rising of temperature so far as 40° C., and often also vomit and increase in peristaltic movements, with excretion of diarrhoic dregs, mixed with blood and, sometimes, acutization of cutaneous preexisting eruptions.

2. The difference in the reaction, due to such inoculation, upon the pellagra patients and upon the sound ones, is so remarkable that there is not appreciable reaction in the latter, in most cases, even if treated with doses eight or ten times stronger than those which are sufficient to provoke an evident reaction with the former.

3. The hypersensibility, which manifests itself in pellagra patients, owing to the inoculation of this watery extract of spoiled maize, has particular characters, which can not be found in any proportion through the injection of extract of sound maize.

4. The active substance, which determines such a reaction of the watery extract of spoiled maize, is obtained by adding a given volume of the grain (deteriorated by mycotic action and not rotten), after having been finely triturated, to three or four volumes of physiological solution of chloride of sodium; by keeping the whole in infusion for six hours in a bagno-marie at 55° C.; by philtering the liquid and by treating it, at last, with twenty times its volume of absolute alcohol. In such a way a precipitation of the active substance is obtained, in white flakes.

5. The thus obtained active substance, to which we have given the name of "pellagrogenina," is soluble in water and not in alcohol; it does not lose its activity at a temperature of 110°–115° C.; it has only a slight degree of poisoning, both for the trial animals and for a sound man; it is, on the contrary, decidedly poisoning for a pellagra patient.

6. The characters of reaction of hypersensibility in the pellagra patient, which evidently result when the watery raw extract of spoiled maize is injected into his body, are more notable, and particularly when the pure pellagrogenina, dissolved in fit quantities of water, is employed. This pure material, when injected into non-pellagra patients, has given no appreciable reaction, in the most experimented cases (90%).

7. The results obtained in more than 100 experiments, which were made with this substance, cause us to consider it of a particular efficiency in the pathogenesis of pellagra, and, in the meanwhile, induce us to propose same as a practical means of anaphylactic reaction for the diagnosis of pellagra.

In order to obtain, to such a purpose, the particular reaction in an appreciable degree, and not dangerous, for the persons suspected to be afflicted with pellagra, the first injection is to be limited to 1 ccm. of

watery solution, sterilized at 100° C., of pure pellagrogenina, at 11 per cent.

If no positive result is obtained by a first injection, this may be experimented with a double dose.

DISCUSSION.

Prof. GAY, California: Prof. Pagliani states in reply to a question that the reaction differs from the tuberculin reaction in that it fails to give a purely local (V. Pirquet) skin reaction in the pellagrin.

A. D. HIRSCHFELDER: I have been much interested in the observations of Prof. Volpino, for two years ago, in the Peoria Insane Asylum, I attacked the same problem by a slightly different method, as it was impossible, for various reasons, to try subcutaneous injections, as I had hoped to do. I tried the cutaneous reaction with extracts of good corn and spoiled corn by the same technique as the v. Pirquet skin puncture of skin. The punctures were made in the skin of the pellagrous area and the corn extract rubbed into the abraded area. Extracts of corn made with 10 per cent NaCe and O.2NaOH, alcohol, and ether were made. In all 13 cases of outspoken pellagra and in 7 cases of individuals who had recovered from pellagra the year before the results were negative. These observations were published in the Archives of Internal Medicine, November, 1900.

M. MOYELL: Prof. Pagliani said in conversation that the diagnostic reaction resembles closely the general reaction to tuberculin injection as used for diagnostic purposes. This extract is injected in minimum dose and is followed soon after by temperature rises, et cetera, a general reaction which he considers specific as a diagnostic test.

Prof. PAGLIANI points out that the injection of this extract causes an augmentation of symptoms. This augmentation, however, passes in a couple of days, and so, when the minimum dose is used, no serious consequences are involved. This diagnotic test is brilliantly successful for the purpose of resolving suspicious diagnosis in suspects.

ZUR FRAGE DER PARATYPHUS-ERKRANKUNGEN.

Von Dr. S. von Unterberger, St. Petersburg.

Die Schilderung des Krankheitsbildes des Typhus gründen wir dem heutigen Stande der Wissenschaft entsprechend auf das ätiologische Prinzip. Vor etwa 50 Jahren wurde der Sammelbegriff Typhus in drei verschiedene Krankheiten geteilt: den Abdominal-, den Fleck- und Rückfallstyphus. Im Jahre 1896 hatten Achard und Bensaude den Paratyphusbazillus entdeckt und das Krankheitsbild des Abdominaltyphus hatte als Erreger, ausser dem Eberth-Gaffkyschen Bazillus, noch andere erhalten, den Paratyphus A und B. Die grosse Bedeutung kommt dem zweiten Erreger zu.

Dass ein Typhus durch verschiedene Erreger erzeugt werden kann, darf uns nicht besonders wundern; wird doch das Bild des Diabetes, Gelenkrheumatismus, Arteriosklerose etc. durch verschiedene auslösende Momente erzeugt.

Die Gruppe Paratyphus lässt sich in zwei Unterabteilungen trennen und zwar in die Paratyphus B Gruppe und in die Gruppe Bac. enteritidis Gärtner. Zur ersten gehören der Schweinepestbazillus, Erreger der Kälberruhr, der Mäusetyphusbazillus (Löffler), Erreger der Pseudotuberkulose bei Meerschweinchen, Erreger der infektiösen Enteritis des Papageien u. s. w. Zur zweiten Gruppe gehören: Bazillen vom Typus Gärtner, gefunden bei Fleischvergiftungen und hiernach beim Menschen, Erreger von infektiöser Rattenenteritis etc. Die beiden Gruppen lassen sich durch spez. Immunitätsreaktionen trennen (Agglutination, Bakteriolyse, aktive Immunisierung, Komplementbildung).

Der Gärtner'sche Bazillus erweist sich vor allem als Erreger der sog. Fleischvergiftung, aber auch bei gastrischen Erscheinungen bis zum Bilde der Cholera ist er gefunden. Makroskopisch lassen sich keine auffällig wahrnehmbaren Veränderungen im Fleisch erkennen. Eine viel seltenere Form der Fleischvergiftung der Botulismus wird durch den B. botulinus erzeugt und ist auch klinisch völlig verschieden.

Ausser Fleischvergiftungen erzeugen diese Bazillen auch Fischvergiftungen und Vergiftungen durch Mehlspeisen, Milchprodukte u. s. w. Mehl kann leicht durch kranke Mäuse infiziert, Massenerkrankungen hervorrufen. Brod kann somit nicht selten ein Erreger der Epidemie werden.

Die Resistenz der Paratyphusbazillen gegen äussere Schädigungen ist im allgemeinen grösser, als diejenige der Eberth'schen Bazillen. Besonders erliegt er der Austrocknung nicht so schnell als dieser. Im Wasser bleibt er namentlich im Schlamm, unter Umständen längere Zeit entwicklungsfähig. Durch Temperatur von etwa 70° wurde er erst nach ungefähr 10 Minuten getötet, was sehr wichtig ist, denn höhere Temp. wie 70° C. werden nämlich im Innern

grösserer Fleischstücke beim Kochen und Braten meist nicht erreicht. Gegen Desinfektionsmittel ist er im allgemeinen etwas resistenter als der Typhusbazillus.

Der Paratyphusbazillus ist im Gegensatz zu dem Typhusbazillus für verschiedene Tierarten ausserordentlich pathogen, namentlich für Meerschweinchen und Mäuse.

Die Paratyphus-Baz.-Infektion der Menschen verläuft meist unter dem Bilde eines Abdominaltyphus und vielfach ist es unmöglich allein auf Grund der klinischen Erscheinungen beide Krankheitsformen von einander abzugrenzen. Für Paratyphus sprechen: plözliches Erbrechen, Schüttelfrost, Herpes, harter Milztumor, Durchfall mit fäkulentem Geruch, flohstichartige Roseola und leichter Verlauf. Bei der Sektion findet man die Darmschleimhaut stark geschwellt, häufig hämorrhagische Follikelschwellungen und Exulzerationen im ganzen Darm, Peyersche Drüsen werden nur leicht geschwellt gefunden. Auch beim Paratyphus finden sich die Erreger in der ersten Krankheitswoche in nahezu 100 Prozent der Fälle im Blute (Gallenanreichung) wie beim Abdominaltyphus.

Die Verbreitungsweise des Paratyphus deckt sich mit der des Abdominaltyphus. Im Vordergrunde steht die Kontakinfektion, ebenso sind Trinkwasserepidemien beobachtet. In den letzten Jahren treten besonders paratyphöse Nahrungs-namentlich Fleischvergiftungen in den Vordergrund, was auf einen Zusammenhang der P.-T.-Infektion des Menschen mit gewissen Erkrankungen des Schlachtviehes hinweist. Viele Bazillen der P.-Gärtner-Gruppe gelangen auf dem Blutwege in die Organe und in das Fleisch der erkrankten Tiere, wo sie sich nach der Schlachtung vermehren und Giftstoff ausscheiden. Makroskopisch lassen sich keine auffällig wahrnehmbaren Veränderungen erkennen. Einwandfreies Fleisch kann nachträglich infiziert werden von kranken Schlachttieren, wenn es zusammen mit kranken aufbewahrt wird und mit infiziertem Wasser und Händen in Berührung kommt, weiter durch Mäuse und Ratten; Fliegen spielen wohl kaum eine Rolle bei der Entstehung von Epidemien.

Auf Grund alles Angeführten kommen wir zu folgenden Schlüssen:

Der Typhus abdominalis (Eberth-Gaffky) und der Paratyphus (Schottmüller) sind in klinischer, pathologisch-anatomischer und bakteriologischer Hinsicht wohl zu trennen und weisen viele Unterschiede auf. Im Grossen und Ganzen ist aber das klinische Bild beider typhösen Krankheiten dasselbe. In pathologisch-anatomischer Beziehung sind bei Paratyphus B. ausser hämorrhagischen Erscheinungen vor allem ein Ergriffensein des ganzen Follikelapparates des Darmes und geringe Infiltration die Peyerschen Drüsen zu verzeichnen. In bakteriologischer Hinsicht ist der Erreger des P. Bazillus biologisch ein ganz anderer, gehört aber auch zur grossen Gruppe der Kolibazillen.

Das alte pathologisch-anatomische Bild des Unterleibstyphus weist ja verschiedene Typen auf: entweder nur exulzerierende Peyersche Drüsen oder neben leichter Infiltration derselben weit verbreitete Follikelinfiltration oder Exulzerationen oder beide Formen zusammen von leichtem und schwerem Grade. Das klinische Bild ist dabei bald sehr schwer, bald mittelschwer, bald sieht man die Krankheit auf den Füssen durchmachen! Wie lassen sich diese Bilder erklären? Wir müssen annehmen, dass in der Mehrzahl aller Abdominaltyphus-Epidemien auch in früheren Jahren stets mitverlief eine Paratyphus-Erkrankung. Die Bazillen der Paratyphusgruppe sind also mit dem Bazillus des Abdominaltyphus stets in Symbiose. Einzelne Epidemien von Paratyphus können wohl durch einen oder wenige Erreger allein vorkommen, aber selten und wenn das der Fall ist, so sind es die Bazillen der Gärtner Gruppe.

Epidemiologisch spielt die Kontakt-Infektion wohl die Hauptrolle und wenn Trink- und Gebrauchswasser infiziert wird, so haben wir meist eine lokalisierte Wasserepidemie. Der kranke Mensch und später der Bazillenträger (bei Paratyphus sind auch jahrelange Dauerausscheider beobachtet) ist der Gegenstand unserer ernsten Sorge bei der Prophylaxe. Brod und Fleisch können Träger der Infektion sein, daher müssen die Mehlspeisen von Mäusen gesäubert werden und das Fleisch stets einer strengen Veterinär-Kontrolle unterliegen. Ausserdem in jeder Handelsstelle die Nahrungsmittel sauber gehalten werden. Fliegen als Verbreiter der Infektion werden wohl wenig in's Gewicht fallen, am meisten noch infiziertes Wasser und Nahrungsmittel.

Bei zwei von mir beobachteten Epidemien fielen auf den Abdominaltyphus ungefähr 30 Prozent auf den Paratyphus B. 20 Prozent und 50 Prozent waren wahrscheinlich infiziert mit weniger virulenten oder abortiven Formen von Bazillen aller drei Gruppen. Gewiss haben, wenn nicht alle so doch die meisten Mannschaften dieses Truppenteils alle Bazillen geschluckt, sind aber nicht infiziert, der Organismus hat sie sofort ausgeschieden.

Wie hätte man in früheren Jahren diese Epidemie genannt? Gewiss, Abdominaltyphus-Epidemie und dabei unterschieden schwere, leichte und ambulatorische Fälle. Nach unseren neuesten Kenntnissen über Paratyphus-Erkrankungen müssen wir solche Typhus-Epidemie für eine Kombination von Eberth, Schottmüller und Gärtnerschen Bazillen erklären, Bazillen die wohl stets in Symboise leben.

Die Hauptaufgabe bei der erfolgreichen Bekämpfung solcher Epidemien muss somit in erster Linie bestehen in der Erziehung zur individuellen Reinlichkeit in des Wortes weitestem Sinne.

Report of a Joint Session of Sections I and VIII will be found in Volume I, Part II.

TRANSACTIONS

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SECTION II.

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REPORT OF THE SECRETARY.

Dr. RUSSELL H. CHITTENDEN, *President Section II,*
Fifteenth International Congress on Hygiene and Demography.

SIR: In accordance with the provision of Article XII of the regulations of the congress I herewith submit a report of the section proceedings of the meeting held at Washington, September 22 to 28, 1912, together with such manuscripts of the papers read as have been delivered into my hands.

MONDAY, SEPTEMBER 23—4.15 P. M.

The first session was called to order by the president, Dr. Chittenden, who announced the following:

Honorary presidents of Section II: Prof. MAX RUBNER (Germany), Prof. ARTUR SCHATTENFROH (Austria), Prof. AXEL HOLST (Norway), Prof. ARCHIBALD B. MACALLUM (Canada).

Reports were then presented for the symposium on the

Physiological Significance of some Substances used in the Preservation of Food, by Dr. John H. Long, professor of chemistry, Northwestern University Medical School, Chicago, Ill., and Dr. Artur Schattenfroh, professor of hygiene in the University of Vienna Austria.

The following members of the congress joined in the discussion: Dr. K. Langenbeck (Boston), Dr. J. H. Long (Chicago), Dr. A. Schattenfroh (Vienna).

TUESDAY, SEPTEMBER 24—9.30 A. M.

President Chittenden and Honorary President Holst presided during the morning session.

Papers were presented in the symposium on the Specific Dynamic Action of Foodstuffs as follows:

The Specific Dynamic Action of Foodstuffs, Dr. Max Rubner, professor of physiology and director of the Physiological Institute, Berlin, Germany.

The Work of Digestion and Specific Dynamic Action, Dr. N. Zuntz, director of the laboratory for animal physiology in the Landwirtschaftliche Hochschule, Berlin, Germany. (Read by Dr. F. G. Benedict.)

The Influence of the Ingestion of Food upon Metabolism, Dr. Francis G. Benedict, director of the nutrition laboratory of the Carnegie Institution of Washington, Boston, Mass.

The Influence of Foodstuffs and their Cleavage Products upon Heat Production, Dr. Graham Lusk, professor of physiology, Cornell University Medical College, New York City.

The following members of the congress joined in the discussion: Dr. K. Langenbeck (Boston), Dr. W. M. Coleman (Washington), Dr. G. Lusk (New York), Dr. Diesing (Hamburg), Dr. M. Rubner (Berlin).

TUESDAY, SEPTEMBER 24—2 P. M.

President Chittenden presided at the afternoon session.

Papers were presented in the symposium on Nutrition and Growth as follows:

An Anatomical Analysis of Growth, Dr. Henry H. Donaldson, the Wistar Institute of Anatomy, Philadelphia, Pa.

Nutrition of the Embryo, Dr. John R. Murlin, assistant professor of physiology, Cornell University Medical College, New York City.

The Nutrition and Growth of Bone. Dr. Francis H. McCrudden, chemist at the hospital of the Rockefeller Institute for Medical Research, New York City.

The Rôle of Proteins in Growth. Dr. Lafayette B. Mendel, professor of physiological chemistry, Sheffield Scientific School of Yale University, New Haven, Conn.

Direct Calorimetry of Infants, with a Comparison of the Results Obtained by this and other Methods. Dr. John Howland, professor of pediatrics, Johns Hopkins University, Baltimore, Md.

The Influence of the Quantity and Quality of Food upon the Growing Organism. Dr. Hans Aron, director of the scientific laboratory of the University Children's Clinic, Breslau, Germany. (Read by Dr. Lafayette B. Mendel.)

WEDNESDAY, SEPTEMBER 25—9.30 A. M.

President Chittenden and Prof. von Noorden presided during the morning session.

Papers were presented in the symposium on the Rôle of Organic Substances in the Nutrition of Man as follows:

The Antagonistic Action of Salts, Dr. Jacques Loeb, Head of the Department of Experimental Biology, Rockefeller Institute for Medical Research, New York City.

The Distribution of Soluble Salts in Living Cells and the Forces Controlling it, Dr. Archibald B. Macallum, Professor of Biochemistry, University of Toronto, Canada.

The Rôle of Common Salt and Water in the Nutrition of Man, Dr. Hermann Strauss, Professor of Clinical Medicine, University of Berlin, Germany.

Additional papers were presented as follows:

On the Nature and Importance of the Diet as the most important factor of causal therapy in severe diseases of the stomach and intestines, in nervous and mental diseases, and in disorders of the circulation and of metabolism, Dr. W. Plönies, Hanover, Germany.

Public Baths, Dr. Simon Baruch, president, American Association for Promoting Hygiene and Public Baths, New York City.

The Significance of Hydrotherapy for Hygiene, Therapeutics and Medical Instruction, Dr. L. Brieger, Hydrotherapeutische Universitäts-Anstalt, Berlin, Germany.

The following members of the congress joined in the discussion: Dr. W. Plönies (Hanover), Dr. J. H. Kellogg (Battle Creek), Dr. S. Baruch (New York).

THURSDAY, SEPTEMBER 26—9.30 A. M.

Honorary President Macallum, Prof. Long, and Prof. von Noorden presided during the morning session.

Papers were presented in the symposium on Practical Dietetics as follows:

Cost and Nutritive Value of Foods, Dr. C. F. Langworthy, Expert in charge of Nutrition Investigations, United States Department of Agriculture, Washington, D. C.

The Choice of Foodstuffs in Relation to Disease, Dr. Carl von Noorden, Professor of Internal Medicine and Director of the I. Medical Clinic, Vienna, Austria.

Diet in Relation to Disease, chiefly in relation to some forms of partial underfeeding (beriberi and scurvy), Dr. Axel Holst, Professor of Hygiene, University of Christiania, Norway.

The Influence of the Preparation of Food on its Nutritive Value, Dr. Max Rubner, professor of physiology and director of the Physiological Institute, Berlin, Germany.

Diet and Metabolism in Fever, Dr. Warren Coleman, Cornell University Medical College, New York City.

The following members of the congress joined in the discussion: Dr. W. Plönies (Hanover), Dr. C. von Noorden (Vienna), Dr. J. H. Long (Chicago), Dr. C. F. Langworthy (Washington), Dr. G. Lusk (New York), Dr. A. Holst (Christiania).

At the close of the discussion an additional paper was presented as follows:

Tuberculosis and Metabolism, Dr. Diesing, chief physician, Recreation and Convalescent Home, Gross-Hansdorf, Hamburg, Germany.

THURSDAY, SEPTEMBER 26—2 P. M.

Honorary President Macallum presided during the afternoon session.

Papers were presented in the symposium on Ventilation in its Hygienic Aspects as follows:

Consideration of the Unknown Factors in the Ill Effects of Bad Ventilation, Dr. Yandell Henderson, professor of physiology, Yale Medical School, New Haven, Conn. (Read by Dr. Lafayette B. Mendel.)

The following members of the congress joined in the discussion: Dr. V. C. Vaughan (Ann Arbor), Dr. T. Hough (Charlottesville).

At the close of the discussion an additional paper was presented as follows:

The Importance of the Nutritive Salts for Healthy and Sick People, Dr. R. Peters, Hanover, Germany.

FRIDAY, SEPTEMBER 27—9.30 A. M.

Honorary President Holst presided during the session.

Papers were presented in the symposium on the Hygienic Physiology of Exercise as follows:

The Influence of Exercise on the Nervous System, Dr. Leon Asher, a. o. professor of physiology, Bern, Switzerland. (Read by Dr. Lafayette B. Mendel.)

The Influence of Exercise on the Heart, Dr. R. Tait McKenzie, director of physical education, University of Pennsylvania, Philadelphia, Pa.

Certain Aspects of the Influence of Muscular Exercise upon the Respiratory System, Dr. Theodore Hough, professor of physiology, University of Virginia, Charlottesville, Va.

Physical Training in the United States Naval Service, Dr. J. A. Murphy, surgeon, United States Navy, United States Naval Academy, Annapolis, Md. (Read by Dr. Smith.)

At the close of the discussion an additional paper was presented as follows:

The Prevention of Arteriosclerosis and Heart Disease in Otherwise Healthy Individuals Past Middle Life, Dr. Louis F. Bishop, New York City.

The Physiological Hygiene of Work in Compressed Air, J. J. R. Macleod, Physiological Department, Western Reserve University, Cleveland, Ohio.

With a few well-chosen remarks, Honorary President Holst then declared the sessions of Section II of the Fifteenth International Congress on Hygiene and Demography closed.

Respectfully submitted.

LAFAYETTE B. MENDEL,
Professor of Physiological Chemistry,
Sheffield Scientific School of Yale University,
New Haven, Conn., Secretary of Section II.

MONDAY, SEPTEMBER 23, 1912.

THE PHYSIOLOGICAL SIGNIFICANCE OF SOME SUBSTANCES USED IN THE PRESERVATION OF FOOD.

By Dr. JOHN H. LONG, Professor of Chemistry, Northwestern University Medical School, Chicago, Ill.

Food preservatives are those substances which delay or prevent the decomposition of food as a result of the action of bacteria or other ferment-producing organisms. Other substances, sometimes classed as preservatives, and in the popular mind associated with them, are not so much preservatives as agents for the conservation of some special property of the food in question, as, for example, the use of copper sulphate in the fixation of the color of green vegetables. A large number of bodies may be included under the head of preservatives, but our interest to-day centers in the so-called artificial or chemical preservatives, because of the question of the permissibility of using them. Some of these bodies have been condemned largely because of their origin, because of their artificial character, which basis of condemnation can not be regarded as sufficient or scientific.

Their merits or faults must be decided on the basis of physiological behavior, essentially, and from this point of view I wish to speak of several substances concerning which the discussions have been the most heated. These discussions will be necessarily brief. First:

SODIUM BENZOATE.

On certain phases of the behavior of sodium benzoate there is an abundant literature. Following the pioneer investigations of Meissner and Shepard, and Bunge and Schmiedeberg, on the synthesis and estimation of hippuric acid, it was recognized that benzoic acid, cinnamic acid, quinic acid, and other bodies are normally combined in the animal organism with glycine and excreted as hippuric acid. It was shown also that many aromatic fruits and vegetables contain these organic acids which go into the benzoyl combination. Numerous later studies have shown the extent of the glycine, or potential glycine, available in the human body for combination.

With the recognition of this normal character of the hippuric acid synthesis, no great objection was raised to the administration of large doses of the benzoate in certain diseases, and, going back some 30 years, we find a considerable record of clinical experience on the

dosage of benzoates in pulmonary tuberculosis, rheumatism, and diphtheria. It was shown by many physicians that doses of 5 to 25 grams a day might be given without apparent harm to the patient. This extended experience was sufficient to show that the toxic effect of the benzoate was of a very low order, not much greater possibly than that of sodium chloride.

At the time when sodium benzoate was considered important therapeutically, the question of its use as a food preservative had not arisen, and the interest attaching to it then, and through the following discussions, was in no wise influenced by the present practical question, To what extent may benzoic acid be combined or detoxified in the animal organism? The earlier observers soon recognized that ordinarily and normally it combines with glycine to form hippuric acid, and the question of the available supply of this amino acid was discussed for a long time. In 1898, in experiments on rabbits, Wiener[1] concluded that while large doses of benzoic acid, about 1.7 grams per kilogram of body weight, were usually fatal, smaller amounts, and up to the quantity yielding 1 gram of hippuric acid per kilogram of body weight, were combined and detoxified. He believed that the value for the combined benzoic acid—that is, the hippuric acid—was rather constant, the maximum being the 1 gram per kilogram of weight. The usual figures were between 0.7821 and 0.8345 gram per kilogram. From this he concluded that the available supply, or stored-up glycine, must amount to 0.3276 to 0.3496 gram per kilogram of weight. He observed that free benzoic acid appeared in the urine when amounts in excess of the maximum values quoted were ingested.

These observations were made at a time when glycine was looked upon as an important intermediary product of protein metabolism and before much was known concerning the quantitative relations of the amino acids in the protein molecule. It was later shown that the mean glycine content of the ingested proteins is not far from 4 per cent of their weight and that the benzoic acid combined to form hippuric acid may be far greater than the weight corresponding to this glycine content. A stored-up reserve of glycine was for a time assumed to account for the remarkable hippuric-acid formation reported by several observers, but this view has been pretty generally abandoned. In this connection the researches of Parker and Lusk,[2] Wiechowski,[3] Cohn,[4] Magnus-Levy,[5] Lewinsky,[6] and others should be referred to. All of these observers found that in the increased ingestion of large amounts of benzoic acid in animals there was an increased protein metabolism, with increasing amounts of the benzoic acid not combined as hippuric acid. In the Lewinski investigations rather large weights of benzoic acid, as the sodium salt, were given to men. In one case a man of 59 kilo-

grams weight took 12 grams of the acid in 12 hours. All was excreted in combined form and no increase of reducing substances in the urine was noted. This amount of acid is nearly one-fifth of a gram per kilogram of body weight, and is relatively less than was ingested in many of the animal experiments. If all combined with glycine it would call for 7.38 grams of the latter, or the glycine existing in about 200 grams of mixed proteins. This amount is probably more than was metabolized in the individual in question.

In another case of Lewinski's a man weighing 67 kilograms took 20 grams of the acid in 12 hours. The urine examination showed the same result as in the other case. Later the same man took 25 grams of the acid, but it was not all combined, as 1.65 grams were recovered from the urine. When the ingestion was increased to 40 grams still more appeared in the urine uncombined with glycine. In one case, on the 40-gram dosage, nausea and headache were noted, but these effects seemed less marked with a diet rich in protein. The author concludes that on a high protein diet more benzoic acid may be ingested without ill effects. In one case a man took 50 grams without apparent disturbance, but over 8 grams appeared in the urine uncombined.

All these experiments demonstrate that in man, as well as in animals, ingested benzoic acid may be deoxified in amounts which much more than correspond to the glycine of protein that may be metabolized normally in the same individual in the same time. The 20 grams of benzoic acid given in one experiment, and which left no free acid in the urine, would correspond to 12.3 grams of glycine.

These papers have been cited because they show the remarkable capacity of the animal organism for the synthesis of hippuric acid and consequent disposition of ingested benzoic acid. It has been shown that the combining power of glycine is not limited to that preformed or which may be split off in the ordinary metabolism, but that in addition the potential glycine of other amino groups is also available, or possibly glycine may be synthetized.

It may be urged that this diversion of potential glycine from more complex acids is in itself an abnormal action and therefore objectionable. This is possibly true and would have weight if we were concerned with the question of ingesting daily 5 grams or more of benzoic acid. But the amounts to be practically considered are so far below this that the question of breaking down extra protein does not come to the front at all.

What amounts of benzoic acid are actually in question here? Practically below 500 milligrams daily if we consider the ordinary solid or semisolid foods, or below a gram a day if we consider certain beverages sometimes treated with benzoate. These are probably extreme figures, as for the great majority of food substances benzoate

is not used or in any sense required. What, then, is the physiological behavior of these small amounts of benzoic acid which have practical significance? Several lines of inquiry may be followed to find an answer to this question, three of which are comparatively direct:

(*a*) The fate in the body.

(*b*) The action on digestive ferments.

(*c*) The action with reference to general health and metabolism.

(*a*) With reference to the relations under (*a*) we have already sufficient information. Small amounts of benzoic acid are completely united with glycine, and for 500 milligrams 307.5 milligrams of the latter are required, an amount far within the liberation from the ordinary protein metabolism. In the cases of infants or invalids with lower metabolism the possible benzoate ingestion is naturally far below this, and there would doubtless be always, even in such extreme cases, a sufficient glycine content for combination.

With no benzoic acid ingested the larger part of the glycine would probably go to form urea and other products by oxidation. With the benzoic acid we have the synthesis of hippuric acid. Unfortunately we have no reliable means of comparing the magnitude of or the difficulty in the enzymic work in the two cases. In certain quarters much has been said about the overburdening of the kidneys with this work of synthesis. As a matter of fact, there is no warrant whatever in the assumption that the tax on the organism is any greater in this case than in the other, and those who make the assumption probably overlook the fact that the hippuric-acid synthesis in the human body is normal and constant. Because of a lack of delicacy in the methods employed for the determination of hippuric acid the quantity of this substance excreted daily has usually been greatly underestimated or neglected entirely.

(*b*) The behavior of benzoic acid toward digestive ferments has been the subject of several investigations. In this direction the action on diastases, pancreatin, pepsin, rennin, and the lipases has been studied. A number of such studies have been carried out in my own laboratory, with the general result that while there is naturally an inhibition of digestive activity with certain concentrations of benzoic acid with those concentrations which have practical importance in the present inquiry the inhibition is very slight or does not appear at all.

In the case of the digestion of starches there is, indeed, a distinct acceleration in the rate of digestion, as is caused by a number of neutral salts and acids of low concentration. This is true not only of digestions by means of malt infusions, but also in the case of taka-diastase and a number of the pancreatic diastase preparations in general use in this country. Similar results were reported some years ago by Leffmann.[7]

While 0.1 per cent of sodium benzoate added to egg-albumen mixture, such as is used in the official pepsin tests, distinctly retards the rate of digestion, this is not the case with one-fifth of this concentration, which is probably above the limit ever found in the stomach after the ingestion of benzoated foods. This relation has been observed in a number of mixtures of fibrin as well as egg albumin and with a variety of pepsin preparations. Analogous results have been reported by Gerlach[8] in his lengthy study of the benzoate question.

Very weak concentrations of either benzoate or benzoic acid have no influence on the rennin coagulation of milk, but with an increase in the concentration there is a gradual inhibition. Our results in this respect are not essentially different from those of Weitzel.[9] In the clinical feeding of infants sodium benzoate has been frequently added to milk.

According to Amberg and Loevenhart[10] the activity of lipase, as measured by the splitting of ethyl butyrate, is not diminished by the presence of 0.1 per cent of sodium benzoate. . Dakin, working in Herter's laboratory, has made a careful redetermination of many of the digestive constants in presence of benzoate.[11]

(*c*) We now come to the most important part of the subject, the behavior of benzoic acid with reference to general health and metabolism. At the time when this substance was extensively used in medical practice—that is, from 1875 to 1880—it was recognized by some physiologists that large doses were followed by increased elimination of nitrogen, which, it was assumed, must come from the breaking down of body proteins. E. Salkowski,[12] especially, from experiments on dogs, concluded that high doses might occasion a considerable loss in man. But in the dog experiments the ingested benzoate amounted in the mean to about one-third of a gram per kilogram of body weight, which proportion, if applied to a man of 50 kilograms weight, would call for nearly 17 grams of benzoate, or 25 grams for a man of 75 kilograms weight. Somewhat similar observations were made by other physiologists, but on the other hand the reports from clinical practice failed to show any such losses. To follow these discrepant observations further is not necessary in this place, as the question of the increased nitrogen excretion has been pretty fully handled in the investigations of Magnus-Levy,[13] Ringer,[14] and Epstein and Bookman,[14] Abderhalden and Hirsch,[15] and others already referred to.

But these early reports have had one very important effect which must be recalled here. They left the impression that the ingestion of sodium benzoate is in general followed by increased protein metabolism, tissue metabolism possibly, an undesirable result, and this statement is frequently repeated as applicable to all doses of benzoate.

A number of lengthy metabolism experiments have shown that for ordinary ingestions of benzoate this increased protein metabolism does not occur. In the last few years the results of several such investigations have been published. One of these investigations was conducted under the auspices of the Bureau of Chemistry of the United States Department of Agriculture, and from it the conclusion was drawn that small doses of benzoic acid or benzoates exert a harmful action on man, a slight loss in weight being affirmed in some cases. It is not my purpose to criticize this work here beyond saying that the published data do not seem to warrant the conclusions drawn, which opinion is shared in a lengthy review of the work by K. B. Lehmann,[16] recently published.

I wish to speak more particularly of the results of the extended studies carried out by Chittenden, Herter, and myself [17] as members of a commission appointed by the Secretary of Agriculture to investigate the question anew. In Herter's work four men were observed through periods of four months, while in the investigations of Chittenden and myself six men on a definite diet containing sodium benzoate were observed through a like period.

These studies covered lengthy observations on the general metabolism of the men, the qualitative changes in the urine, the effects on the blood, effects on the intestinal flora, and daily clinical observations on the weight and general condition of the men. Under the head of metabolism determinations were made of the nitrogen balance and utilization, the distribution of nitrogen, the distribution of sulphur, and the utilization of fat. From the data of Chittenden and myself, which were fuller in detail than those of our colleague, certain facts are clearly shown. In Chittenden's series of experiments the doses of benzoate were administered as follows:

Fore period (14 days)	No benzoate
Low benzoate period (62 days)	300 milligrams daily
After period (10 days)	No benzoate
Medium benzoate period (7 days)	600 milligrams daily
First high benzoate period (7 days)	1,000 milligrams daily
Second high benzoate period (7 days)	2,000 milligrams daily
Third high benzoate period (7 days)	4,000 milligrams daily
After period (10 days)	No benzoate
Total (124 days)	71.8 grams

This is an average dosage of 718 milligrams daily for dosage periods. In my series of experiments the amounts were as follows:

Fore period (25 days)	No benzoate
Low benzoate period (60 days)	300 milligrams daily
Medium benzoate period (14 days)	600 milligrams daily
High benzoate period (18 days)	1,000 milligrams daily
After period (7 days)	No benzoate
Total (124 days)	44.4 grams

This is equivalent to an average dosage of nearly 483 milligrams daily for the dosage periods. In either case the dosage more than covers the practical consumption and is doubtless better adapted to throw light on the subject than are the excessive doses previously given. Large ingestions of benzoate are no more suited to prove its practical physiological action than would 150 grams of sodium chloride, kilograms of sugar, or half liters of vinegar daily be suitable for these substances. With such large ingestions even the common food substances or condiments might be made to appear highly injurious.

Time will not permit me to go into details with reference to all these experiments. It is sufficient to say that no effects whatever were observed which pointed to a modification of the nitrogen or fat utilization, the nitrogen balance or distribution, the sulphur metabolism, the body weight or the hemoglobin content and red and white counts in the blood. The order of nitrogen distribution remained always the same in the period averages, and it was only when doses of 4 grams of benzoate daily were given that Chittenden noticed a slight, but to be expected, percentage decrease in the urea excretion.

Qualitative changes in the urine.—In all of our work frequent examinations were made for the appearance of sugar or other reducing bodies, traces of albumin, casts, aromatic oxyacids, or other things which might indicate a change in the nature of the excreted bodies. There was never any indication of an alteration in this direction. The occasional appearance of a trace of albumin or of a hyaline cast was no more frequent in the dosage periods than in the fore periods, and was without practical significance.

During the progress of the work frequent determinations were made of the so-called normal reduction of the urine of the men working in my laboratory, by means of a delicate ammoniacal copper solution. No definite changes were noted which could be connected in any way with the benzoate. After the conclusion of the 124 days of regular experimentation two of the men in my group, who had followed the regular routine, continued for seven days longer, with higher dosage. They began with 5 grams a day and finished with 10 grams, the average being 7.5 grams daily. With this large dosage there was no reduction which could be noticed with Fehling solution, and nothing which was outside the normal limits for the ammoniacal solution, although there appeared to be a slight increase from the former figures. Other changes were absent. A third man who had not been a member of the experimental squad, but who had followed the same diet routine, took doses beginning with 5 grams and ending with 7.5 grams on the seventh day. No abnormal behavior of any description was noted in his excretion or general condition. In this

case it could not be urged that the man had become accustomed to large doses through gradually increasing small doses.

Temperature, pulse, respiration.—All these factors were systematically noted from day to day for each man. Absolutely no variations from the normal were observed which might in any way be attributed to or connected with the dosage of benzoate.

Conclusions.—From all these observations the conclusion was drawn that in the dosage administered, which is large enough for practical purposes, sodium benzoate exercises no recognizable physiological action on the human organism, beyond the slight increase in hippuric acid excretion, a change which is often exceeded after hearty meals of certain berries and fruits which are frequently consumed in quantity. I have recited the facts in some detail because of the long-continued and persistent attempts to create the impression, especially in this country, that sodium benzoate exerts a toxic action sufficiently marked to warrant its exclusion from use with foods.

Gerlach's studies.—Attention must be called here to an elaborate investigation carried out by Dr. Gerlach, of Wiesbaden, on the effects of sodium benzoate as used in the food industries. These experiments were continued through a long period and appear to have been conducted with great care. From the numerous clinical and metabolism observations made, Dr. Gerlach draws the conclusion that sodium benzoate causes no changes in the body which may be considered as harmful, or which may be taken as pointing to a departure from the normal in any direction.[18]

COPPER SALTS.

It has long been a popular notion that copper salts are decidedly toxic, and the older medical literature contains many references to poisoning by verdigris and other combinations of copper. Modern study, however, has shown that these assumed effects were greatly exaggerated. The subject has practical interest now because of the custom, which had its origin in France, apparently, of fixing the color of certain green vegetables by cooking them, in the canning process, in contact with small amounts of copper sulphate or other copper salt. The effect depends on the formation of a very stable green compound of copper and a derivative of chlorophyll.

The permissibility of the process has been much debated, especially in France, Germany, and Belgium. In France the discussion has been a prolonged one and several scientific commissions have taken part in it. Some of the older commissions made reports, finding against the use of copper in this way, but in the more recent studies the results seemed to point to the practical harmlessness of the metal

in green peas and beans. In consequence of these French investigations, and later ones in Germany, the use of copper in limited amounts is now tolerated by the food laws of most European countries.

There seems to be no question regarding the physiological action of relatively large amounts of copper salts. They behave as irritant poisons, and produce nausea, vomiting, and purgation, while the small quantities absorbed exhibit characteristic lesions in the liver, spleen, kidneys, and other organs. We are concerned, however, with amounts far below those necessary to cause any such violent symptoms, amounts which could scarcely exceed 15 to 20 milligrams of copper daily in any case, and usually much below this. In the coloring of peas and beans the amount of sulphate used is generally less than 1 gram per kilo, a part only of which becomes fixed in the product, the actual copper content being from 25 to 150 milligrams per kilo, ordinarily.

What are the effects of small doses, up to 20 milligrams, of copper daily? To answer this question experiments have usually been made with the sulphate or other soluble salt, but it should be recognized that this does not exactly correspond to the practical situation, since in the pea or bean the copper is largely combined as phyllocyanin compound, which in its solubility is very different from the ordinary salts, and is much more stable.

The results of a long series of experiments carried out in my laboratory in the last two years have convinced me that the copper *perfectly* combined in this chlorophyll derivative is practically without any evident physiological action in amounts up to 12 or 15 milligrams daily, which amounts would be contained in a weight of the vegetable as large as any one could eat with a relish for more than a short period. There appears to be no effect on body weight, nitrogen metabolism, blood factors, or qualitative or microscopic blood findings. Nausea is not produced. But the case is somewhat different when we turn to small doses of copper salts given in tea, coffee, milk, or beer. Here in time we notice some effect, especially in causing nausea and digestive disturbances, and also in some cases a slight modification of the nitrogen partition and some of the blood factors.

In young vegetables with high chlorophyll content the copper sulphate used in small amount appears to be very perfectly combined. This compound is remarkably stable, and resists the action of the digestive ferments to a degree which prevents any great absorption of the copper. In the case of the green pea, especially, the chlorophyll is largely in the hulls, and these, still green with their copper compound, may pass through the alimentary tract and be found in the feces but little changed. This copper-chlorophyll complex is but slowly broken up by hydrogen sulphide or ammonium sulphide.

In older vegetables, however, where the chlorophyll has become considerably destroyed, this copper compound can not be formed to the same extent, and the copper added in the canning operation goes into a union with proteins, which is easily broken down. In this case the copper acts much as it does in the ordinary inorganic salts. In experiments, I have found it possible to add 250 to 300 milligrams of copper per kilo to old green peas, and others have reported still higher additions. Much of this copper may be separated easily by dilute hydrochloric acid.

The fact that the nonionic copper in the phyllocyanate is practically inert physiologically has been noticed by others. Reference here may be made to the work of Tschirsch,[19] Spiro,[20] Brandl.[21] These writers agree that other compounds of copper have a much more marked effect. From these other combinations, as well as from imperfectly coppered vegetables, the metal may reach the liver and other organs and in time produce a marked effect. In a series of experiments by Chittenden this absorption has been clearly shown. As long as it is not practically possible to limit the use of copper in greening to the youngest vegetables only, and in a specified small amount, it would seem that it might be well to prohibit its use altogether in foods where, indeed, it serves no useful purpose beyond imparting a bright green color.

SULPHUROUS ACID.

Sulphurous acid is used in two essentially different ways in the treatment of food products. First, in the free state or the oxide, and, secondly, as a salt, usually sodium sulphite, but sometimes the bisulphite. Some years ago there was for a time a limited application of the true hyposulphite, but this seems to have been abandoned. Sulphurous acid found its first uses in this connection in the protection of must before fermentation and in the racking off or transfer of wines from one vat to another or just before bottling. These uses are still in vogue and other uses have been introduced, especially in the clarification of cane juices before boiling down for sugar and in the treatment of certain fruits in the sun-drying process. Within comparatively recent times the application of sodium sulphite in some of the minor meat industries and in the canning of certain vegetables was introduced.

It will be seen at a glance that we have here two rather distinct conditions. In the application of the sulphurous acid in the sugar, wine, and fruit industries there is finally a pretty complete combination of the product with the sugars to form the aldehyde compounds, from which the sulphite is gradually oxidized. These carbohydrate-containing substances hold also certain organic salts, the

acids of which are in part displaced by the sulphurous acid. The protein and fatty substances of meats, however, are in themselves inert toward sodium sulphite and the latter remains unmodified or combined. The fats, in addition, protect the sulphite from rapid oxidation. Among food chemists there seems to be a practical recognition of this distinction in the active condition of the two classes of sulphured products, and the question of permissibility of use has been advanced generally with reference to the sulphites rather than as concerns the carbohydrate combinations.

As observed with relatively large ingestions, all these products exert, of course, a somewhat toxic action, and the toxicity of the carbohydrate combinations seems to run parallel with their rates of dissociation as aldehyde compounds. For the pure aldehydes the rate is rather rapid in the glucose compound, as the lengthy investigations carried out by Rost and Franz and by Kerp [22] have shown. But in their experiments the rate of dissociation of the glucose aldehyde compound is undoubtedly far greater than would be the case in the commercial combinations of fruits and sirups, for example where there is always a great protecting excess of the sugar present. In most of the experiments carried out to test the pharmacological action the dosage of the sulphur compound has been so relatively large as to render difficult a conclusion regarding the behavior of small doses, or those which have practical importance. This is especially true of the experiments of Kionka,[23] frequently quoted.

In Lehmann's experiments on dogs and cats, with doses running up to 37.5 and 62 milligrams of sulphurous oxide (150 to 250 milligrams of sulphite) daily, and extending through about 200 days, no definite harmful effects were seen. Lehmann [24] considered these doses relatively large.

I can refer but briefly to the work of two recent French commissions which have studied the behavior of sulphurous acid in wine, with respect to the health of the consumer. As a result of these investigations an official announcement was made about a year ago in France advancing the allowable content of sulphurous oxide in wine from 350 to 450 milligrams per liter, of which not over 100 milligrams may be in the free state. I have not heard that this tentative standard has been modified.

This whole question is now under review by the commission appointed by the Secretary of Agriculture of this country, but the lengthy investigations undertaken have not yet been brought to a conclusion, and can not, therefore, be discussed here.

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[8] Wiesbaden, 1909.
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[13] Loc. cit.
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[15] Zeits. phys. Chem. 78.
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[17] Report No. 88, United States Department of Agriculture, 1909.
[18] Dr. med. V. Gerlach, Physiologische Wirkungen der Benzoesaeure und des benzoesauren Natron. Wiesbaden, 1909.
[19] Das Kupfer vom Standpunkte der gerichtlichen Chemie, Toxikologie, und Hygiene. Stuttgart, 1893.
[20] Muench. Med. Wochenschr. *56*, I, 1070.
[21] Arb. aus dem kais. Gesundheitsamt, 1897, *13*, 104.
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[24] Arch. Hygiene, 1909, *66*, 303.

DIE PHYSIOLOGISCHE BEDEUTUNG EINIGER SUBSTANZEN FÜR DIE KONSERVIERUNG DER NAHRUNGSMITTEL.

Von Dr. ARTUR SCHATTENFROH, Professor der Hygiene an der Wiener Universität (Österreich).

Die Konservierung der Nahrungsmittel durch Zusatz bestimmter, die Mikrobientätigkeit hemmender Substanzen beansprucht für den Hygieniker immer ein hohes Mass von Interesse. Es darf daher nicht Wunder nehmen und kann wohl der allgemeinen Zustimmung sicher sein, dass die Kongressleitung das Thema, das erst am letzten hygienischen Kongresse in Berlin verhandelt wurde, neuerlich zur Diskussion stellt. Die Absicht, immer wieder das Schädliche und Unzuträgliche konservierender Zusätze zu Lebensmitteln von hygienischen Gesichtspunken zu beleuchten, erscheint mehr denn je als begründet und zeitgemäss. Gewinnen doch leider die Bestrebungen derjenigen immer mehr an Boden, die aus Gewinnsucht, Gleichgiltigkeit oder Unverstand—direkt und indirekt—die Verbreitung der Konservierungsmittel fördernd, den hygienischen Postulaten gegenüber sich ablehnend verhalten.

Wenn ich daran gehe, einen kurzen Überblick über das umfangreiche Gebiet zu geben, so halte ich es aus mehrfachen Gründen für angezeigt, die Anlehnung, an das vortreffliche Berliner Referat von v. Gruber, Lehmann und Paul zu suchen. Insbesondere der allgemeine Teil der Schlusssätze der genannten Autoren präzisiert in so klarer Form und ganz ohne Einschränkung giltig die Anschauungen der

Hygieniker, dass man kaum in der Lage ist, irgend etwas Wesentliches hinzuzufügen. Ich möchte nur auf folgendes besonders aufmerksam machen.

Bei der Beurteilung eines Konservierungsmittels taucht zunächst die Frage auf, ob dasselbe bei ein- oder mehrmaliger Aufnahme, insbesondere aber bei häufigem oder regelmässigem Genusse des damit versetzten Nahrungsmittels, für den Menschen gesundheitsschädlich sei, und da erscheinen in erster Linie die Toxikologen berufen, auf Grund ihrer Erfahrungen und geeigneter Experimente die richtige Antwort zu geben. In Wirklichgeit können sich aber die Fragestellung und die Methodik der pharmakodynamischen Forschungsrichtung nur ausnahmsweise dem tatsächlichen Bedürfnisse anpassen und diese wird daher nur selten den Hygieniker befriedigende Aufschlüsse bringen. Der Unterschied zwischen pharmakologischer und hygienischer Beurteilung einer einem Nahrungsmittel zugesetzten fremden Substanz, z. B. eines Konservierungsmittels ist nicht nur darin gelegen, dass die hygienische Betrachtung des Gegenstandes viel weitere Gesichtspunkte sucht und auch nach den Schäden fragt, die der Zusatz des Stoffes indirekt bervorruft—wie Verdeckung der minderen Qualität des Nahrungsmittels, des Verderbs, Förderung einer bestimmten nachteiligen Zersetzung, Unterdrückung der "physiologischen" Bakterienflora, etc. etc.—auch der Begriff der Gesundheitsschädlichkeit scheint für den hygienischen Fachmann ein ganz anderer zu sein, wie für den Toxikologen.

Die Definition des Begriffes "gesundheitsschädlich" im weiteren Sinne unterliegt gewiss nicht geringen Schwierigkeiten, da ja die physiologische Breite der Gesundheit eine ziemlich grosse ist und auch individuell recht verschieden begrenzt wird. Es kann aber keinem Zweifel unterliegen, dass sich "gesundheitsschädlich" und "giftig" nicht decken, eher wäre es zutreffend, alle jene Stoffe, welche "different" sind, als gesundheitsgefährlich zu bezeichnen. Mitunter freilich rufen differente Stoffe von stärkster spezifischer Giftigkeit bei medizinaler Anwendung scheinbar keine Gesundheitsstörungen hervor, sondern leiten sogar Heilungsvorgänge ein. Es geht aber gewiss nicht an, wollte man von solchen Substanzen, die zu Heilzwecken dienen, behaupten, dass sie aus diesem Grunde nicht gesundheitsschädlich sein können und wollte man speziell die medizinale Dosis als unterhalb jener liegend ansehen, die als gesundheitsschädlich zu gelten hat. Gerade das Gegenteil trifft zu.

Gesundheitsschädlich ist offenbar der viel weitere Begriff als giftig, auch wenn man geneigt ist, letzteren Terminus nicht so eng zu begrenzen, wie es gewöhnlich geschieht.

Eine besondere Schwierigkeit ist darin gelegen, dass es keineswegs immer gelingt, in speziellen Fällen durch das Menschen- oder Tier-

experiment die vorliegende Frage zu lösen, es wäre denn, dass es sich um exquisit giftige Stoffe handelt. Auch in Beobachtung im Grossen lässt im Stich, da die Gesundheitsstörungen, die durch die in der Regel kleinen Dosen differenter Stoffe herbeigeführt werden, nur ausnahmsweise so prompt und turbulent auftreten, dass ihre ursächliche Beziehung zu dem genossenen Stoff klar liegt.

Jedenfalls müssen wir vom Standpunkte der hygienischen Fürsorge für den Konsumenten mindes tens verlangen, dass alle fremdartigen Zusätze zu Nahrungsmitteln insolange als unzulässig erklärt werden, als nicht ihre völlige Unschädlichkeit erwiesen ist—und mag diese Forderung nach dem eben Auseinandergesetzten auch als eine strenge und schwer zu erfüllende gelten, so ist eine zweite doch mit um so grösserem Nachdruck zu stellen und auch leichter zu erreichen: "Substanzen, die im Menschen- oder Tierversuch bei beliebiger Anwendung als different erkannt sind, sollten als Zusätze zu menschlichen Nahrungs- und Genussmitteln auch in kleinsten Dosen nicht zugelassen werden." Grenzzahlen—hierin stimme ich dem Referate von v. Gruber, Lehmann und Paul durchaus bei—sind grundsätzlich zu verwerfen, da sie nicht kontrollierbar sind und sind nur in Ausnahmsfällen zu dulden.

Einer kurzen Erörterung bedarf die Deklaration für Konservierungsmittel. Die Forderung, dass derartige Zusätze zu Nahrungsmitteln obligatorisch durch den Deklarationszwang gekennzeichnet werden, ist gewiss an sich wohl begründet, ja man könnte sagen, dass sie aus logischen Gründen gestellt werden muss. Tatsächlich aber ist ihre Durchführung nicht zu gewärtigen, da die Deklaration erfahrungsgemäss nur im Grosshandel geübt wird und im Detailhandel verschwindet. Die Deklaration dient demnach in der Regel nur als Deckmantel für die Fälschungen der unlauteren Grossproduktion, die ihre Erzeugnisse unbekümmert unter Deklaration in den Handel bringt, da sie nicht zu fürchten braucht, dass dieser die Ware als unverkäuflich erklärt und zurückweist. Der Detailhändler löst die verräterische Hülle und das Publikum erfährt nichts von der Metamorphose.

Die Deklaration ist kein Schutz für die Konsumenten und sie darf demnach niemals, das kann nicht stark genug betont werden, als eine ausreichende Gewähr dafür angesehen werden, dass das Publikum nicht übervorteilt wird.

Unter gar keinen Umständen darf aber die Deklaration als eine genügende Sicherung angesehen werden, wenn es sich um Zusätze handelt, die nach der Art des angewendeten Präparats als nicht unbedenklich gelten. In diesen Fällen ist die Deklaration, soferne man

annehmen wollte, dass sie geübt wird, geradezu schädlich, denn das Publikum wird beim Erkennen des deklarierten Zusatzes im Vertrauen auf die öffentliche Controlle der Lebensmittel der Meinung sein, dass es sich um harmlose Substanzen handelt, die aus irgend welchen technischen Rücksichten dem Lebensmittel beigemengt werden.

Für den Gesetzgeber bedeutet aber ein derartiges Vorgehen eine scheinheilige Handlung, indem er es der Urteilskraft des einzelnen überlässt, seine Entscheidung ze treffenfi selbst aber den Mut nicht aufbringt, den bedenklichen Zusatz zu verbieten. So lässt sich die Notwendigkeit nachstehender Forderung gewiss nicht bezweifeln: "Der Zusatz eines als different erkannten Konservierungsmittels zu einem Lebensmittel darf nicht dann als zulässig angesehen werden, wenn er deklariert wird. In einem solchen Falle ist die Deklaration geradezu als schädlich anzushe."

Am Schlusse dieser allgemeinen Erörterungen möchte ich die Aufmerksamkeit der Fachmänner noch auf folgenden Punkt lenken. Gelegentlich wird behauptet, dass der Zusatz eines Konservierungsmittels oder ähnlichen Stoffes zu einem Lebensmittel nicht erfolge, um dasselbe haltbar zu machen (wie ja in den meisten Fällen), oder um es dem Geschmacke des Publikums entsprechend zu schönen (wie z. B. beim Kupfern konservierter grüner Gemüse), sondern die Erzielung einer ganz bestimmten Qualität bezwecke und in diesem Sinne, wenn diese letztere eine beim Publikum beliebte Handelsware betrifft, unentbehrlich und daher zu tolerieren sei.

Mir schwebt hier vor allem das Beispiel der geschwefelten Görzer Prunellen vor, deren Begutachtung jüngst den österreichischen Obersten Sanitätsrat in eingehender Beratung beschäftigte.

Es wird von Devarda, einem ausgezeichneten Kenner der Produktionsverhältnisse, die Behauptung aufgestellt, dass die landesübliche Schwefelung der Prunellen in der Umgebung von Görz, die von den Bauern in äusserst primitiver Weise durch Verbrennen von Schwefel unter den Obsthürden vorgenommen wird, für das gewonnene Produkt von ausschlaggebender Bedeutung sei. Nicht oder nicht ausreichend geschwefelte Prunellen seien missfärbig, trocken und auch bei weitem nicht so schmackhaft. Devarda ist geneigt, für diesen Einfluss der schwefligen Säure auf das Fruchtfleisch chemische Wirkungen anzunehmen, die sich im Gefolge des Schwefelungsprozesses während des nachfolgenden Trocknens und Reifens der Konserven abspielen. Es erscheint eine solche Vermutung von vornherein als nicht unbegründet. Es ist sehr wohl möglich, dass das fertige, übliche Produkt bei den gegenwärtig verfügbaren Einrichtungen ohne reichliche Schwefelung nicht erzielt werden kann und

es kann in der Tat hier eine chemische oder physikalisch-chemische Wirkung der schwefeligen Säure vorliegen. Für die hygienische Beurteilung erwachsen aus solchen Tatsachen mitunter ausserordentliche Schwierigkeiten, da die Macht der Produktion und die handelspolitischen Einflüsse häufig genug höher veranschlagt werden als die fachmännischen Überlegungen. Hier handelt es sich eben um Machtfragen. Das fachmännische Urteil kann aber begreiflicherweise davon nicht berührt werden. Sind solche, die Qualität eines Lebensmittels in irgend einer Weise beeinflussende und bestimmende Zusätze nicht völlig unschädlich, so sind sie ebenso wie jene eines konservierenden Stoffes als unzulässig zu erklären und Publikum und Produktion müssen trachten, ihre Wünsche der neuen Situation anzupassen.

In dem erwähnten Falle hat denn auch der Oberste Sanitätsrat mit grosser Majorität diesen Standpunkt eingenommen.

Ich will nun im speziellen Teil meines Referates die Wirkungen einzelner wichtigerer Konservierungsmittel in Betracht ziehen.

AMEISENSÄURE.

Die konservierende Wirkung der Ameisensäure zeigt sich nach Croner, Seligmann und Proskauer bereits in 0.15 prozentigen Lösungen (gegen Hefepilze und Milchsäurebakterien), nach Fleig ist die antiseptische Wirkung der Ameisensäure äusserst schwach.

Von den toxikologischen Wirkungen interessieren für die vorliegende Frage begreiflicherweise nur jene, welche der per os verabreichten Ameisensäure zukommen. Versuche am Menschen wurden in letzter Zeit (1906) nur von Kallmann und Lebbin angestellt, die feststellten, dass ihre Versuchspersonen durch mehrere Wochen täglich ½ Liter Himbeersaftlimonade unter Zusatz von 0.5 g Ameisensäure ohne Beschwerden und ohne Nierenschädigung zu sich nahmen.

Aus den Tierversuchen ergibt sich im Wesentlichen folgendes: Grössere Mengen bewirken Nierenschädigung, die auf Säurewirkung zu beziehen ist. Formiate verbrennen zu Bicarbonaten und machen den Harn alkalisch, werden aber auch zum Teil unverändert mit dem Harn ausgeschieden. Bei stomachaler Einführung wird ein Teil der Ameisensäure bereits im Verdauungstrakte unter Mitwirkung der intestinalen Mikrobienflora in H_2 und CO_2 zersetzt (Fleig, 1907 und 1908). Geringe Mengen von Ameisensäure wirken antidiastatisch, in grössern Dosen vermehren sie Sekretion und Peristaltik (Fleig).

Die Ameisensäure ist kein spezifisches Herzgift. Ob sie Methämoglobin im Körper bildet, ist nach den Versuchen von Rost, Franz und Heise wieder fraglich geworden, ebenso ob eine kumulative Wirkung kleiner Dosen angenommen werden darf. Nach Heffter

und Rubner wirkt die Ameisensäure nach Art der organischen Säuren, aber stärker ätzend als Essigsäure. In Verdünnungen wirkt sie schädigend auf die Schleimhaut des Magendarmkanals und bei Zufuhr grösserer Mengen auch auf die Nieren.

BORSÄURE UND BORAX.

Auch nach neueren Versuchen an Hunden (Puppe) sowie nach der Anschauung der wissenschaftlichen Deputation für das deutsche Medizinalwesen und auf Grund der Arbeiten von Forster müssen Borsäure und Borax selbst in kleinen Dosen als Stoffwechselgifte angesehen werden, nachdem der Meinungsstreit zwischen Liebreich und Gerlach einerseits und Wiley, Rost, Kister und Hoffmann anderseits wohl zu gunsten der letzteren Auffassung als entschieden gelten darf. Die Verwendung von Borsäure und Borax zur Nahrungsmittelkonservierung ist zweifellos unzulässig.

SCHWEFLIGE SÄURE.

Das unselige Rundschreiben des deutschen Reichskanzlers, das die Duldung von 1200 mg schwefliger Säure in 1 Kg Dörrobst anordnet, hat in der fachmännischen Beurteilung der vorliegenden Frage einigermassen verwirrend gewirkt und wohl auch überrascht. Machen sich doch schon 600 mg durch den unangenehmen, kratzenden Geschmack bemerkbar. Nach hygienischen Begriffen ist auch die amerikanische Grenzzahl (350 mg pro Kg Dörrobst) weit zu hoch gegriffen. Das Argument, das für die Berechtigung so hoher Zusätze in der Regal angeführt wird, dass es sich nicht um freie schweflige Säure, sondern um glukoseschweflige Säure handle, ist nicht stichhältig, da die letztere lose Verbindung ungemein leicht dissoziiert. Dies geht schon daraus hervor, dass freie schweflige Säure neben glukoschwefliger Säure jodometrisch nicht bestimmt werden kann, indem in dem Masse, als die freie Säure oxydiert wird, die gebundene Säure dissoziiert (im Gegensatz zu der viel beständigeren aldehydschwefligen Säure).

Mehr geschadet als genützt haben die Versuche Kionka's an Hunden, bei denen die Verfütterung kleiner Dosen von Sulfiten angeblich schwere innere Blutungen auslöste. Lehmann und Trentlein, die bei exakter Nachprüfung die Kionka'schen Versuchsresultate an Hunden und Katzen nicht bestätigen konnten, neigen infolge dessen zur Annahme, dass kleine Mengen schwefliger Säure im Körper rasch oxydiert würden und daher unschädlich seien. Diesbezügliche Versuche an Menschen, die in diesem Sinne sprächen, wurden aber von den Autoren nicht ausgeführt.

Es scheint mir, dass die Versuchsergebnisse von Wallbaum und Jacoby, nach denen 10–50 mg schwefliger Säure bei Menschen gesund-

heitsschädlich wirkten, bisher zu Recht beständen und durch Tierversuche in ihrer Beweiskraft nicht erschüttert werden können.

Aber auch die anderen bisher in der Literatur verzeichneten Menschenversuche mit schwefliger Säure (Polli, Bernatzik und Braun, Pfeiffer, Lench, Lebbin & Kallmann, Lehmann (1901), Marischler, Wiley, Sonntag und Franz, Höppener) sprechen in ihrer Gesammtheit keineswegs zu gunsten der Unschädlichkeit der schwefligen Säure für den Menschen. Vom toxikologischen Standpunkte aus wäre es immerhin erwünscht an einer grösseren Anzahl von Menschen die Giftwirkung der schwefligen Säure des näheren zu erforschen, in hygienischer Hinischt darf wohl angenommen werden, dass die Unzulässigkeit des Zusatzes von schwefliger Säure zu Lebensmitteln nicht länger zu bezweifeln ist.

SALICYLSÄURE.

Die Ergebnisse der Versuche von Wiley an Menschen (1906), in denen die Mehrzahl der Versuchspersonen durch fortgesetzten Genuss kleiner Dosen von Salicylsäure ungünstig beeinflusst wurde, haben gewiss an Beweiskraft nichts eingebüsst, wenngleich im allgemeinen Christian (1908) zugestimmt werden kann, dass Dosen unter 0.1 g Salicylsäure die normalen Functionen des Körpers nicht alterieren.

Sehr beachtenswert ist die relativ starke Wirkung der Salicylsäure auf kranke Nieren und bei der grossen Verbreitung von Nierenaffektionen ist auf diesen Umstand, wie schon Lehmann betont, Gewicht zu legen.

BENZOESÄURE.

Das Hauptinteresse an den Wirkungen der Benzoesäure wandte sich auch in den letzten Jahren vorwiegend der Frage zu, wie sich bei Benzoesäuredarreichung die Ausscheidung dieser Substanz bewegt und wie weit die Bildung des Paarlings der Benzoesäure in Hippursäuremolekül, des Glykokolls, durch die Benzoesäurezufuhr beeinflusst wird (Mangus-Levy, Seo, Lewinski, H. D. Dakin).

Es scheint, dass relativ sehr grosse Mengen von Benzoesäure fast restlos als Hippursäure ausgeschieden werden können, wobei allerdings der zur Glykokollbildung nötige Stickstoff dem Eiweissbestand des Körpers entzogen werden muss, wenn der Nahrungsstickstoff hiezu nicht ausreicht. Bemerkenswert ist, dass Benzoesäure im Harn auch infolge Spaltung der ausgeschiedenen Hippursäure—durch Bakterien oder Fermente—auftreten kann. Nierenkranke scheiden die Hippursäure unvollkommen aus, bilden sie aber anscheinend in unverminderter Menge. Friedmann & Tachau fanden, dass die Hippursäure-Synthese bei Kaninchen in der Leber erfolgt,

Sei nun der Genuss der Essigsäure schädlich oder nicht, lässt sich irgend wie daraus die Berechtigung ableiten, Zusätze anderer schädlicher Stoffe zu Lebensmitteln zu rechtfertigen? Zeigt nicht das Beispiel der alkoholischen Getränke, wie unrichtig es ist, aus der fast allgemein verbreiteten Trinksitte auf die Unschädlichkeit des Alkohols zu schliessen und ist es nicht sattsam bekannt, wie schwer sich solche Gewohnheiten ausmerzen lassen?

Wir fürchten, dass der Zusatz von konservierenden Stoffen zu Nahrungsmitteln häufig den Verkehr mit minderwertigen Produkten erleichtert, aber nicht in dem Sinne, dass das Konservierungsmittel durch seinen Eigengeruch oder Eigengeschmack die auffallenden Eigenschaften des Nahrungsmittels verdeckt. Das "Schönen" der Nahrungsmittel durch den konservierenden Zusatz und die Beeinflussung der sinnfälligen Zersetzung jener durch das Konservierungsmittel haben in der Regel eine ganz andere Bedeutung und sind keineswegs in Analogie zu setzen mit den Geschmack- und Geruchwirkungen des Essigs und der Gewürze.

Natürlich können auch diese das Erkennen nachteiliger oder minderwertiger Eigenschaften eines Nahrungsmittels verhindern.

TUESDAY MORNING, SEPTEMBER 24, 1912.

DIE SPEZIFISCH-DYNAMISCHE WIRKUNG DER NÄHRSTOFFE.

By Dr. MAX RUBNER, professor of physiology and director of the Physiological Institute, Berlin, Germany.

Merkwürdigerweise hat man in der ältern Stoffwechsellehre nie daran gedacht, zu untersuchen, ob der Effekt der Ernährung nicht auch von der Temperatur bei welcher ein Versuch angestellt werden war, mit abhängig sei. Ich bin durch ein genaues Studium meiner Experimente dahin geführt worden, diesen Gedanken einer Rückwirkung der Wärmeänderungen auf die Ernährungsvorgänge zu studieren, wobei sich in hohem Masse interessante Consequenzen ergeben haben.

Es war zunächst mir aufgefallen, dass man durch Fütterung grösserer Nahrungsmengen vor allem von Eiweiss eine Steigerung der Wärmeproduktion gegenüber dem Hungerzustande herbeiführen kann; wenn aber eine solche Steigerung vorhanden ist, so sagte ich mir, muss die Wärmeregulation verändert sein, denn Steigerung der Verbrennung bedeutet Wärmeüberschuss und letztere bedeutet für den Wärmeabfluss genau das gleiche, als wenn wir die Wärme der Umgebung soweit gesteigert hätten, dass eine Verminderung der Wärmeabgabe herbeigeführt wird. Der Körper muss aber bei Zunahme der Wärme der Umgebung bei innerer Wärmebildung schon früher in den Zustand der Entbehrlichkeit der chemischen Regulation gelangen. Dies hat sich auch als richtig erwiesen. Tatsächlich befanden sich solche Tiere durch die Nahrung meist in einem Zustand der physikalischen Regulation, eine von der Nahrung ausgehende Wärmebildung hatte die früheren Leistungen der chemischen Regulation übernommen. Die im Herrschungsbereich der chemischen Regulation nur selten auftretende Vermehrung der Wärmebildung nach Nahrungsaufnahme über die Grenzen der Hungerzersetzung hinaus lässt sich aber in voller Stärke und Reinheit dar zeigen, wenn man von vornherein die chemische Wärmeregulation durch die Wahl einer höheren Lufttemperatur ausgeschaltet hat.

In der Tat lässt sich leicht beweisen, dass im Zustande der physikalischen Regulation bei Tieren alle Nahrungsstoffe eine Steigerung des Energieverbrauches herbeiführen, welche für ausschliessliche Ernährung mit Rohrzucker + 5.8 Prozent für Fett + 12.7 Prozent für Eiweisstoff + 30.9 Prozent beträgt. Ich nenne diese Werte, die spezifisch dynamische Wirkung.

Um in ein völliges Nahrungsgleichgewicht zu kommen, muss man noch erheblich mehr an Stoffen zuführen, als den Werten der spezifisch dynamischen Wirkung selbst entspricht. Setzt man den Energieverbrauch im Hunger = 100, so tritt bei Eiweiss ein Gleichgewicht ein bei 140.2; bei Fett Gleichgewicht ein bei 114.5; bei Rohrzucker Gleichgewicht ein bei 106.4.

Bei Experimenten mit Mischungen der Nahrungsstoffe stimmten die Wirkungen etwa auf eine Summierung nur bei Eiweiss und Fett; bei Mischungen von Eiweiss, Fett und Kohlenhydraten wurde stets auch in länger dauernden Versuchen etwas weniger Wärmesteigerung gefunden, als einer Summation der Wirkung der einzelnen Komponenten entsprach; doch waren die Unterschiede im Verhältnis zum Gesamtstoffwechsel recht klein.

Die spezifisch dynamische Wirkung einer gewöhnlichen gemischten Kost des Menschen beträgt 7–8 Prozent mehr Wärmebildung, als sie dem Hungerzustand entspricht.

Die durch die spezifisch dynamische Wirkung erzeugte Erhöhung der Wärmebildung wird durch gleichzeitige Arbeitsleistung nicht verändert.

Die spezifisch dynamischen Wirkungen sind bei den Tieren nicht aufzufinden gewesen, solange ich bei niederen Temperaturen 12–15° den Ernährungsversuch ausführte, da gelten streng die isodynamen Werte. Die Unterschiede kommen aber in voller Grösse zum Ausdruck, wenn man das Experiment bei 30–33° anstellt. Für gewöhnlich sind diese besonderen Wirkungen der Nährstoffe, die ich die spezifisch dynamische Wirkung nannte—durch die chemische Wärmeregulation compensiert. Diese letztere braucht umso weniger zu leisten, je grösser die spezifisch dynamische Wirkung einer Substanz ist.

Bei niederer Lufttemperatur lässt sich der Organismus leicht durch eine Nahrung in Gleichgewicht bringen, welche genau seinem Verbrauch im Hungerzustande entspricht. Bei hoher Temperatur gelingt dies nicht, oder doch erst mit einem erheblichen Ueberschuss der einzuführenden Energie.

Soweit die Tatsachen, die leicht nachzuprüfen sind. Die Erklärung dieser besonderen Wirkung der Nährstoffe ist aber nicht ganz leicht. Als ich die ersten Versuche dieser Art machte (1885); die aber noch nicht mit voller Ausschaltung der chemischen Wärmeregulation angestellt waren, dachte ich mir den Einfluss der Nahrung als eine Anregung der drüsigen Teile des Körpers durch die Verdauung. Nichts schien mir selbstverständlicher, als dass eben die Nahrungsaufnahme und Verdauung, die ja sichtlich die Tätigkeit in den Drüsen des Nahrungsschlauches steigert durch einen vermehrten Umsatz in allen dabei beschäftigten Zellen die Steigerung der Wärmeproduktion herbeiführt, in gleichem Masse war dann eine

Wärmemehrbildung für wärmeregulatorische Zwecke entbehrlich. Es war das eine "Kompensationstheorie" gegründet auf die gegenseitigen Beziehungen zwischen spezifisch dynamischer Wirkung und Wärmeregulation. Als ich aber 1902 die Versuche mit völliger Ausschaltung der chemischen Regulation wieder aufnahm, und die ganze spezifisch dynamische Wirkung unverküsst vor mir sah, überzeugte ich mich, dass meine frühere Theorie zur Erklärung nicht ausreichte. Die 8–10 Prozent Verdauungsorgane, die wir im Körper finden, können doch nicht den ganzen Kraftwechsel des Körpers bei Eiweiss um 31 Prozent der Tageswerte steigern.

Es kamen ja in meinen Versuchen nur die leichtest resorbierbaren Nahrungsstoffe in Betracht. Bei einem Pflanzenfresser, der eine nur langsam zu verdauende Kost aufnimmt, liegen natürlich die Verhältnisse anders. Warum sollen sich auch so enorme Unterschiede bei den einzelnen Nahrungsstoffen finden? Warum der in Wasser leicht lösliche Zucker überhaupt eine besondere Drüsenarbeit in Anspruch nehmen? Es war mir weiter bekannt, dass die Aufnahme, selbst grosser Flüssigkeitsmengen ohne eine Aenderung des Energiebedarfs verläuft, dass weiterhin auch die Resorption von Fleischextractivstoffen, von denen wir wissen dass sie anregend auf die Verdauungsdrüsen wirken, gleichfalls eine Steigerung der Wärmeproduktion vermissen lassen. Ich machte dann noch ferner die Beobachtung, dass bei der Steigerung der Eiweisszersetzung im protrahierten Hungerzustand und bei Phlorhizindiabetes also ohne Resorptionsvorgänge, wobei Eiweiss eingeschmolzen und direkt in den Säftestrom kommt, doch die spezifisch dynamische Wirkung sichtbar wird. Ich habe daher an eine andere Hypothese der Erklärung denken müssen. Natürlich wäre es widersinnig annehmen zu wollen, dass bei hohen Temperaturen der Umgebung das Energiebedürfnis der Zelle selbst plötzlich und spezifisch eine anderes werden sollte, wie bei niederer Umgebungstemperatur, also kann man nur voraussetzen, dass der Mehrverbrauch an Energie darauf zurückführen ist, dass diese Energie der Nahrungsstoffe nicht für die lebende Substanz gleich verwertbar ist.

In welcher Form aber braucht die lebende Substanz die Energie?

Die Frage ist leichter negative zu beantworten als positiv. Sicher ist es, dass die in den Spannkräften der Nahrung eingeführte Energie nicht direkt als Wärme auftreten darf, auch nicht als Elektrizität.

Soll ich sie aber im positiven Sinne beantworten, so kann ich mich am verständlichsten ausdrücken, wenn ich Ihnen in Kürze meine Anschauung vom Ablauf des Lebensprozesses auseinandersetze.

Die lebende Substanz, als deren kleinste Teilchen ich "Bionten" annehme, ist eine labile Verbindung, welche sich selbst überlassen unter Wärmeentwicklung zugrunde geht, wenn sie nicht rechtzeitig

mit neuer Energie versorgt wird. Diese Energie besorgt sie sich aus den nährenden Molekülen, die sie durch bestimmte fermentative "Seitenketten" wenn wir diesen Ausdruck wählen wollen, zerlegt. Für die Haupttypen der Nahrungsstoffe sind solche besondere Fermentwirkungen anzunehmen. Zerfällt das ernährende Molekül, so gewinnt die lebende Kraft einen kleinen Zuwachs an Energie, der sich im ganzen Gebiete des "Bionten" fühlbar macht, also eine Aenderung der Stellung der Moleküle oder auch Atome zur Folge hat. Der nächste, nach aussen hin fühlbar werdende Effekt besteht in der Annulierung der Fermentwirkung. Hat ein Zuckermolekül Kraft an die lebende Substanz abgegeben, so findet vorläufig auch kein Zerlegung von Fett und keine Zerlegung des stickstofffreien Anteils des Eiweisses statt, erst dann, wenn durch Abgabe von Energie aus dem Bionten (sei es mechanische Kraft, wie bei der Muskeltätigkeit, sei es Wärme) seine molekularen und atomaren Aufbau ändert, erscheinen wieder die Fermentwirkungen und neues Nahrungsmaterial wird zerlegt. Der Anlauf der Lebenszeit also ein Kreisprozess mit variablen Fermentwirkungen, das Ganze geleitet durch Selbstregulation nach isodynamen Prinzip.

Die Zelle kann netterisch also nur jene Energie verwenden, die im Momente ihrer Entwicklung aus der Spannkraft der Nahrungsstoffe der lebenden Substanz ihre Kraft zur Verfügung stellt.

Es ist aber sicher, dass im Organismus neben jenen echt vitalen Vorgängen der Energieversorgung der lebenden Substanz auch Prozesse fermentativen Charakters oder chemische Umsetzungen ausserhalb der Aktionsphäre der lebenden Substanz unter Wärmeentwicklung verlaufen. Man darf dabei aber nicht an die fermentativen Vorgänge bei der Verdauung etwa denken. Gewiss liefert die Invertierung der Disaccharate in Monosaccharaten, die Unwandlung der Stärke in Glykose, die Fettspaltung etwas Wärme aber gerade die Aufspaltung des Eiweisses in die tryptischen Produkte verlüfte wie Grafe in meinem Laboratorium gezeigt hat, thermisch indifferent. Aus diesem ganzen Gebiete der Wirksamkeit der Verdauungsfermente kann ein nennenswerter Betrag eines Energieverlustes nicht abgeleitet werden. Ich denke mehr an die Prozesse der intermediären Zersetzung.

Ich möchte sogar sagen, ohne die Annahme solcher gelegentlichen Nebenprozesse ist uns der komplizierte Ablauf der Zersetzungen im Tierleib überhaupt garnicht denkbar, ja es würde nach moderner Auffassung des intermediären Stoffwechsels gerade als ein unerträglicher Zwang und eine Schwierigkeit empfunden werden, wenn man die ganze Stoffwechselgleichung kontinuierlich in engster Verbindung mit der lebenden Substanz sich denken müsste.

Intermediäre und rein thermochemisch verlaufende Umsetzungen sind gerade beim Eiweiss und bei den N-haltigen Stoffen dieser

Gruppe am wahrscheinlichsten. Ich habe auch zeigen können, dass sich spezifisch dynamische Wirkung nicht nur auf echtes Eiweiss, sondern auch auf den Leim erstreckt.

Die Spaltung der N-haltigen Nährstoffe im Körper erfolgt sicher, wie Fick zuerst annahm, so dass ein N-freier Körper der später oder direkt zu Zucker oder Glykose wird, und andererseits ein N-haltiger Rest sich abtrennt, der allmählicher weiter abgebaut wird; das letztere geschieht durch verschiedene fermentative Umwandlungen, stufenweise im intermediären Stoffwechsel, wobei zweifellos freie Wärme auftritt. Diese Theorie experimentell zu beweisen, dazu fehlen uns freilich die Mittel, aber es gibt eine ganze Anzahl von Argumenten, die für sie sprechen. Wenn man z. B. die verschiedenen maximalen Angaben über Zuckerbildung oder Glykogenbildung am Eiweiss besonders jene von Lusk betrachtet und voraussetzt, dass diese Kohlenhydrategruppen das energetisch Wirksame im Eiweiss sind, so kommt man sehr nahe auf solche Relationen der Energieverwertung wie sie in der spezifisch dynamischen Wirkung ausgedrückt sind. Und weiter ist es durchaus denkbar dass neben den Zuckergruppen sich Aminosäuren und dergl. abspalten, die allmählich in Harnstoff übergeführt werden. Bei einem solchen Abbau ist es thermochemisch durchaus möglich, dass die dabei freiwerdende Wärme jenem im physikalischen Regulationszustand unverwertbaren Energieanteil entspricht. Auch für Fette und Kohlenhydrate wird vorausgesetzt, dass ihr Abbau ein stufenweiser wenn auch nicht so komplizierter wie jener des Eiweisses sei.

Mit dieser Theorie steht die schon eben mitgeteilte Tatsache, dass auch die gleichzeitige Arbeitsleistung nichts an der spezifisch dynamischen Wirkung ändert, gut im Einklang. Ich habe auch erwähnt, dass Mischungen von mehreren Nahrungsstoffen immer eine etwas kleinere spezifisch dynamische Wirkung gegeben haben, als sich durch Summierung der Einzelwirkungen berechnen lässt. In allen solchen Fällen handelt es sich bei meinen Versuchen um kleine Eiweissmengen, daher wird auch ein erheblicher Anteil des aufgenommenen Eiweisses zum Ersatz der Abnützungsquote genommen. Man begreift, dass es dabei nicht jene Veränderungen erfährt, die zu einer spezifisch dynamischen Wirkung führen können.

Wenn nun auch der ganz überwiegende Teil der spezifisch dynamischen Wirkung auf die eben geschilderten Veränderungen der Nährstoffe im intermediären Stoffwechsel zurückgeführt werden muss, so will ich natürlich nicht leugnen dass ein paar Prozente des ganzen Prozesses vielleicht auch auf andere Vorgänge entfallen kann.

In allen drei Fällen bei Eiweiss, Fett, und Kohlenhydraten kann vielleicht ein kleiner Teil des Energieverlustes schon durch Fäulnis und Gärung in den Darm eintreten, jedwede Einwirkung auf die Drüsen des Darms absolut zu leugnen, habe ich auch keinen Grund.

Ich bin aber der Anschauung, dass verschiedentlich solch eine Wirkung überschätzt wird, und dass ein experimenteller Nachweis kleiner Veränderungen in der Tätigkeit von Zellgebieten welche zum Verdauungsgebiete gohören, schwierig, vielleicht unmöglich sein kann. Ich will die Gründe kurz auseinandersetzen. Jeder wird anerkennen müssen, dass die Tätigkeit der Verdauungsdrüsen natürlich auch den Verbrauch von Nahrungsstoffen steigern wird. Die übliche Kalkulation ist aber die, dass man bei allen Betrachtungen über die Verdauung immer sämmtliche Fällen Komplexe ins Auge fasst, welche auch nur grob anatomisch irgendwie Beziehung zum Nahrungsrohr besitzen. Diese Annahme schiesst zweifellos über das Ziel hinaus, denn wir können z. B. mit Bestimmtheit sagen, dass die Funktionen der Leber oder des Pankreases doch nicht einzig und allein der Verdauung dienen, sondern auch noch anderen Zwecken. Auch über den substantiellen Aufwand von Stoffen für Verdauungszwecke und für die Verdauungssäftebereitung hat man oft ganz übertriebene Vorstellungen ausgesprochen. In der Drüsenzelle müssen wie in jeder Zelle energetische Prozesse ablaufen, weil diese die Vorbedingung aktiven Lebens sind, ausserdem aber müssen wir wegen der Sekretbildung (Galle, Magen, Speichel, Darmsaft, Pankreassaft) bei den Drüsen des Verdauungsapparates voraussetzen, dass namentlich die N-haltigen Bestandteile an dem energetischen Stoffwechsel teilnehmen, also bei der Tätigkeit in den täglichen Ausscheidungen in erheblicherem Masse auftreten und nachweisbar sind. Trotz aller dieser Verdauungsfunktionen kann man bei Zuckernahrung ohne besondere Schwierigkeit die N-Ausscheidung des Organismus so stark erniedrigen, dass sie oft nur $\frac{1}{3}$ der Hunger-N-Ausscheidung, wo es garnichts zu verdauen gibt, ausmacht. Die echt stofflichen Bedürfnisse müssen also für Verdauungszwecke im engeren Sinne einen sehr beschränkten Umfang haben. Für die Schätzung der Drüsenarbeit wird ferner oft die starke Blutverschiebung nach den Unterleibsorganen zur Zeit der Verdauung geltend gemacht, aber nicht immer bedacht dass eine solche selbst bei einem völligen Mangel an Verdauungsarbeit bloss für einfache Flüssigkeitsresorption erforderlich sein kann.

Meiner Meinung nach könnte ein Mehrverbrauch bescheidener Art in Verhältnis zum Gesamtstoffwechsel auch vorhanden sein, ohne, dass sich ein solcher in der Kohlensäureausscheidung, der Sauerstoffausscheidung, im Stickstoffverlust zu äussern brauchte. Ich denke dabei an die Möglichkeit einer kompensatorischen Verschleierung der erhöhten Tätigkeit eines Organs durch die Herabsetzung des Stoffwechsels eines anderen. Diese Annahme steht freilich nicht im Einklang mit der Meinung mancher anderer Autoren, welche als selbstverständlich voraussetzen, dass alle Organe unter sich ein fest abgestuftes Verhältnis ihrer Minimalleistung haben,

dass sie, alle auf dieses Minimum eingestellt, auch ein Minimum des Stoffwechsels des ganzen Organismus bedingen, während jede noch so geringe Vermehrung der Tätigkeit in einem beliebigen Organ einen Zuwachs im O-Konsum, der Kohlensäureausscheidung, der Mehrerzeugung von Wärme liefern. Ich kann nicht finden, dass diese Anschauung einwandsfrei bewiesen wäre, solange man selbst bei manchen Organen annehmen muss, dass sie mehreren Funktionen dienen, welche nicht alle gleichzeitig im Körper beansprucht werden, kann es sich auch um eine innere Kompensation der Tätigkeit, also um das Brachliegen von Zellgruppen handeln, während andere ihre Tätigkeit vermehren. Ebenso ist sicher auf Grund der Blutfülle eines Organes häufig eine Blutabnahme in anderen verhanden, sodass auch dabei durch Kompensation im Organismus nach aussen hin die wahre Leistung vermindert oder ganz verdeckt erscheint.

Man hat auch andere Hypothesen zur Erklärung der spezifisch dynamischen Wirkung aufgestellt. Zuntz hat früher namentlich an der Hypothese einer mechanisch gedachten Darmarbeit festgehalten und sie dann ähnlich erweitert wie dies in meiner Kompensationstheorie älteren Datums geschildert wurde, die natürlich auch immer das missliche hatte, dass man keinen Grund einsieht, warum das an sich wertvolle Eiweiss für die Resorption so enorme Arbeitsleistung verursachen sollte. Neuerdings hat Zuntz einen alten Gedanken von Fick aufgenommen und die Aenderung der respiratorischen Grössen beim Tier und beim Menschen nach Harnstoffzufuhr geprüft, wobei sehr erhebliche Steigerungen der O-Aufnahme zutage getreten sind. Aus diesen Experimenten lassen sich aber so enorme Steigungen des Kraftwechsels ableiten, dass diese weit mehr ausmachen, als die gesamte spezifisch dynamische Wirkung überhaupt. Es ist an sich in höchstem Masse unwahrscheinlich und unverständlich, wenn für eine so untergeordnete Funktion wie die Eliminierung von Harnstoff der Körper soviel Energieaufwand notwendig haben sollte. Kürzlich hat übrigens auch Fangl gezeigt, dass die Niere während der Tätigkeit keinen nennenswerten Energieaufwand nötig hat, und dass auch deshalb die Versuche von Zuntz nicht auf Nierenarbeit zurückgeführt werden können. Ich kann daher nicht finden, dass eine andere bessere Theorie der spezifisch dynamischen Wirkung meine bisherige Auffassung zu ersetzen in der Lage wäre. Der Ernährung im Zustande der physikalischen Regulation hätte für die Theorie der Ernährung im Ganzen genommen, also die Bedeutung, dass sie zwischen den energetischen Hauptprozess und einigen thermischen Nebenprozessen im Organismus zu scheiden erlaubt.

DIE VERDAUUNGSFÄHIGKEIT UND DIE SPEZIFISCH DYNAMISCHE WIRKUNG DER NAHRSTOFFE.

By Dr. N. ZUNTZ, Professor an der landwirtschaftlichen Hochschule, Berlin, Germany.

Das Thema meines Referats: Work of Digestion and Specific Dynamic Action ist in dem deutschen Programm unrichtig wiedergegeben. Es muss heissen: "Die Verdauungstätigkeit und die spezifisch dynamische Wirkung der Nährstoffe."

Da ich persönlich auf dem Kongress nicht anwesend sein kann, möchte ich das Thema nicht ausführlich bearbeiten, vielmehr nur das hervorheben, was meine und meiner Schüler Arbeiten zu seiner Klärung beigetragen haben und bei dieser Gelegenheit gewisse irrtümliche Deutungen, welche meine Arbeiten erfahren haben, berichtigen.

Als ich im Jahre 1877 im Verein mit von Mering[1] den Einfluss der Nahrungszufuhr auf die Oxydationsprozesse im Tierkörper zu untersuchen begann, hatte man von einer Vertretung der Nährstoffe im Verhältnis ihrer Verbrennungswärme keine einigermassen präzise Vorstellung. Man beachtete vor allen Dingen jene Ergebnisse der Pettenkofer-Voitschen Respirationsversuche, welche sehr erhebliche Unterschiede in der Kohlensäureproduktion bei verschiedener Ernährung aufgewiesen hatten. Wie wenig die Vorstellung, dass ein neu zugeführtes Nahrungsmittel die Rolle anderer vorher umgesetzter im Stoffwechsel übernehme, Gemeingut der Physiologen war, geht unter anderem aus den Fragestellungen hervor, welche den Arbeiten des Ludwigschen Laboratoriums aus jener Zeit zu Grunde lagen. Unter Benutzung des speziell durch Kowalewsky ausgearbeiteten Respirationsapparates für kleine Tiere liess Ludwig durch seine Schüler die Frage untersuchen, welche Nährstoffe bei Zufuhr ins Blut im Organismus verbrannt würden. Er glaubte, dass nur solche Stoffe der Verbrennung unterliegen, nach deren Zufuhr der Sauerstoffverbrauch anstieg. Er dachte also nicht an eine Vertretung von Körperbestandteilen durch den neu zugeführten Stoff, sondern an eine richtige Luxuskonsumption desselben. In dieser Weise kam Scheremetjewsky zu dem Schluss, dass milchsaures Natron im Blute verbrannt werde, denn nach seiner Zufuhr stieg der Sauerstoffverbrauch, dass aber Zucker nicht oxydiert werde, weil seine Zufuhr ins Blut keine Steigerung des Sauerstoffverbrauchs zur Folge hatte. Man nahm daher an, dass der Zucker erst irgendwelche Umwandlung im Verdauungsapparat erfahren müsse, ehe er im Körper oxydiert würde. Bei der Nachprüfung dieser Arbeiten fanden von Mering und ich, dass auch milchsaures Alkali, wenn es in vorsichtiger Weise in die Blutbahn gebracht wird, den Sauerstoffbedarf nicht nennenswert steigert, dass es sich also in der Hinsicht ähnlich wie Zucker herhält. Dass die intravenös zugeführten Stoffe oxydiert wurden

konnten wir aber mit Sicherheit feststellen dadurch, dass sich der respiratorische Quotient in dem Sinne ändert, wie bei Verbrennung der eingeführten Substanz erwartet werden musste. Nur bei wenigen Nährstoffen, insbesondere bei den Produkten der Magenverdauung des Fibrin konnten wir eine erhebliche Steigerung der Verbrennungsprozesse auch bei intravenöser Zufuhr nachweisen. Dieselben Stoffe, welche intravenös zugeführt ohne Steigerung des Sauerstoffverbrauchs, also im wesentlichen auch ohne einen erhöhten Energieumsatz verbrannt wurden, bewirkten eine Steigerung des Verbrauchs, wenn sie auf dem natürlichen Wege durch den Magen gegeben wurden. Hieraus schlossen wir, dass die Verdauung mit einer Steigerung das Stoffwechsels deshalb verbunden sei, weil sie eine Arbeitsleistung des Organismus bedeutet. Diese Arbeitsleistung besteht in gesteigerter Bewegung des Darmkanals, erhöhter Tätigkeit seiner Drüsen und, im Dienste der heirfür nötigen reichlicheren Blutversorgung, vergrösserter Arbeit des Herzens. Die Richtigkeit unserer Befunde, resp. die Deutung derselben wurde von Voit energisch bestritten, und ihm schloss sich Rubner an, nachdem er in seinen berühmten Versuchen über die Vertretungswerte der Nährstoffe gefunden hatte, dass unter gewissen Umständen der Stoffwechsel des hungernden Tieres nicht steigt, wenn man ihm eine zur Erhaltung ausreichende Nahrungsmenge zuführt, dass es also Bedingungen gibt, unter denen auch bei Zufuhr der Nahrung per os dieselbe Konstanz des Energieumsatzes besteht, welche wir bei intravenöser Zufuhr beobachtet hatten. Rubner hat später selbst sein von dem unsrigen abweichendes Ergebnis dadurch befriedigend erklärt, dass er zeigte, dass seine hungernden Tiere sich im Zustande der chemischen Wärmeregulation befanden, d. h. dass ihr Stoffwechsel behufs Erhaltung der Körpertemperatur gesteigert war. Diese Steigerung wurde nach Nahrungszufuhr durch die erhöhte Wärmeproduktion, welche die Verdauungsarbeit bedingte, unnötig und fiel weg. Als Rubner später seine Hunde bei einer Temperatur von 30° C. untersuchte, bei welcher keine chemische Wärmeregulation besteht, fand auch er nach jeder Zufuhr von Nahrung eine Steigerung der Verbrennungsprozesse, wie wir sie bei unseren im warmen Bade gehaltenen Kaninchen gefunden hatten. Er schloss sich zunächst unseren Anschauungen mit geringer Modifikation an, indem er die Steigerung auf "Drüsenarbeit" bezog. Später aber wollte er deren Bedeutung nicht mehr anerkennen, glaubte vielmehr, dass es sich namentlich bei den Eiweisskörpern um Wirkungen handle, welche dadurch zustande kämen, dass ein Teil der Abbauprodukte für die Kraftleistungen des Körpers nicht brauchbar sei. Er nannte jetzt diese Wirkungen der Nährstoffe, welche auf der Unbrauchbarkeit gewisser Bestandteile für dynamische Leistungen des Körpers beruhe, "spezifisch dynamische Wirkungen." Ich glaube durch die neueren, in meinem

Laboratorium ausgeführten Versuche nachgewiesen zu haben, dass der Teil der Stoffwechselsteigerung, welcher unabhängig von der Verdauungsarbeit ist, und den Mering und ich zuerst nach intravenöser Zufuhr von Eiweiss festgestellt haben, auf einer ganzen Reihe von Ursachen beruht, von denen einige wenigstens jetzt mit Sicherheit charakterisiert werden können. Dass die Arbeitsleistung des Verdauungsapparates je nach der chemischen und mechanischen Beschaffenheit der Nahrung eine sehr verschiedene Energiemenge beansprucht, konnten wir durch Versuche über die Bedeutung der mechanischen Beschaffenheit der Nahrung für die Grösse der Energieproduktion nachweisen. Tierarzt Müller[2] zeigte durch zahlreiche Respirationsversuche, dass dieselbe Menge Kohlehydrate in Form von Stärke etwa 3 Prozent mehr Energie erfordert, als wenn man sie als Traubenzucker dem Tier zu fressen gibt. Für die Eiweisskörper konnte Steck[3] nachweisen, dass die Nierentätigkeit nicht unwesentlich an dem durch sie bedingten erhöhten Stoffwechsel beteiligt ist. Dies zeigte sich darin, dass auch grössere Mengen Harnstoff, ebenso wie Chlornatrium, eine Steigerung der Verbrennungsprozesse in erheblichem Umfange sowohl bei Menschen wie bei Hunden herbeiführten.

Noch genauer sind diese Verhältnisse durch Tangl[4] und seine Schüler an kurarisierten Tieren studiert worden. Sie bestätigen den nicht unerheblichen Anteil der gesteigerten Nierenarbeit am Stoffwechselzuwachs nach Eiweisskörpern, zeigen aber ausserdem eine eigentümliche Art spezifisch dynamischer Wirkung, indem auch nach Entfernung der Nieren Harnstoffzufuhr eine, wenn auch geringere, Steigerung des Stoffwechsels bewirkt.

Den Einfluss der mechanischen Beschaffenheit der Nahrung und der mit ihr wechselnden Grösse der Arbeit der Darmmuskulatur demonstrierten Hagemann und ich[5] am Pferde, dessen Energiebedarf proportional der Menge Pflanzenfaser, welche das Tier mit seiner Nahrung aufnahm, anstieg.

Ähnliche Wirkungen beobachtete Magnus-Levy bei Hunden, denen er grössere Mengen von Knochen verfütterte.

In jüngster Zeit hat Dahm[6] dieselbe Beziehung zwischen Menge der Rohfaser und Grösse des Energiebedarfs beim Rinde nachgewiesen.

Zu gleichen Ergebnissen kam Hagemann und durch besonders sorgfältig ausgeführte Untersuchungen Ustjanzew bei Schafen.[7]

Ein scheinbar wichtiges Argument gegen die Bedeutung der Muskelarbeit des Darmes für die Höhe der Umsetzungen im Tierkörper lieferten die Untersuchungen von Cohnheim am ausgeschnittenen Tierdarm, welcher bei lebhafter Peristaltik nur einen geringen Sauerstoffverbrauch ergab. Dieses Resultat dürfte aber

damit zusammenhängen, dass Cohnheims Därme widerstandslos arbeiteten. Wie bei den quergestreiften Muskeln und wie beim Herzen muss auch bei der glatten Muskulatur des Darmkanals der Energieaufwand für die Arbeit mit der Belastung, d. h. in diesem Falle mit der Schwierigkeit, die Inhaltsmassen weiter zu bewegen, wachsen. Dass die vom Darm unter einigermassen normaler Belastung geleistete Arbeit eine sehr erhebliche ist, sieht man bei der von Rona in jüngster Zeit ausgebildeten Methodik. (Nach einer gütigen Angabe von Rona leistet 1 g Kaninchendarm stundenlang eine mechanische Arbeit von 60 gm per Stunde. Das muss, wenn die Verwertung des Sauerstoffs für die Arbeit ebenso gross ist wie beim quergestreiften Muskel bei 1.7 kg. Gericht des menschlichen Darmkanals 150 ccm. O_2-Verbrauch pro Stunde bedingen.)

Ein weiteres bei der spezifisch dynamischen Wirkung der Nährstoffe in Betracht kommendes Moment sind anregende Wirkungen, welche mit der Nahrung aufgenommene Stoffe auf diese oder jene Zellgruppe des Körpers ausüben. Es sei in der Hinsicht nur an die Wirkung der Schilddrüsensubstanz auf die Oxydationsprozesse erinnert, ferner an die Wirkungen der Ovarialsubstanz, welche Loewy und andere studiert haben. Neu in dieser Reihe von Tatsachen ist ein anderweit noch nicht veröffentlichter Fund, welchen Dr. Schirokich in jüngster Zeit in meinem Laboratorium erhoben hat. Er studierte die Einwirkung von Pentosen, speziell der Arabinose, auf Stoffumsatz und Sauerstoffverbrauch. Bei Hunden kann Arabinose nur in mässigen Mengen (nicht über 15 g) bei einem Tier von 8 kg verabreicht werden, weil sonst heftiger Durchfall auftritt. Ungefähr die Hälfte der verfütterten Arabinose erschien im Lauf der nächsten 12 Stunden im Harn. Trotzdem tritt eine kleine Sparwirkung auf den Eiweissumsatz ein. Was aber das Bemerkenswerteste ist, der respiratorische Gaswechsel, speziell der Sauerstoffverbrauch sinkt um etwa 5 Prozent unter den Hungerwert. Viel frappanter tritt die durch Arabinose bewirkte Herabsetzung der Oxydationen beim gleichmässig gefütterten Tiere zu Tage. Es handelt sich hier also um einen Einfluss, der den bisher beobachteten Wirkungen von Nährstoffen der Richtung nach entgegengesetzt ist.

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[1] von Mering u. Zuntz: Inwiefern beeinflusst Nahrungszufuhr die tierischen Oxydationsprozesse? Pflüger's Arch., 15, 634, 1817, und ebenda, 32, 173, 1883; ferner Wolfers, ebenda, 222; Potthast, ebenda, 280; Albert Lilienfeld, ebenda, 293. In letzterer Arbeit und bei Zuntz Gesichtspunkte zur Kritik der neueren Arbeiten auf dem Gebiete der Ernährung; Landw, Jahrbücher 8, 65, 1879) sind die energetischen Gesichtspunkte erörtert. Rubners Abhandlung, Die Vertretungswerte der hauptsächlichsten Nahrungsstoffe im Tierkörper, 1883, Zeit, für Biol., 19, 313.

[2] Uber die Verdauungsarbeit nach Kohlehydratnahrung in ihrer Abhängigkeit Verhandl. d. physiol. Ges. zu Berlin, 10. Dec. 1909, abgedruckt Medic. Klinik, Bd. 28, H. 5–6.

[3] Verdauungsarbeit und specifisch dynamische Wirkung der Nahrungsmittel. Verhandl. d. physiol. Ges. zu Berlin, 10. Dec. 1909, abgedruckt Medic. Klinik, Jahrg., 1910.

[4] Tangl: Die Arbeit der Nieren und die "spezifisch-dynamische Wirkung" der Nährstoffe. Biochem. Zeitschr., Bd. 34, H. 1.

[5] Zuntz, Hagemann u. Lehmann: Stoffwechsel des Pferdes, Berlin, Parey, 1898. S. 275 ff.

[6] K. Dahm: Die Bedeutung des machanischen Teils der Verdauungsarbeit für den Stoffwechsel des Rindes. Bioch. Zeitsch., —— Bd. 28, H. 1–2.

[7] W. Ustjanzew: Die energetischen Äquivalente der Verdauungsarbeit bei den Wiederkäuern. Biochem. Zeitschr., Bd. 37.

THE INFLUENCE OF THE INGESTION OF FOOD UPON METABOLISM.

Dr. FRANCIS G. BENEDICT, Director of the Nutrition Laboratory, Carnegie Institution.

Experimenters are uniformly agreed upon the observed fact that following the ingestion of food there is an increased metabolism as measured either directly by the heat production or indirectly by the gaseous exchange. The cause of this increased heat production is capable of several interpretations. Based upon a series of experiments made with his assistant v. Mehring, the experiments of Loewy on the ingestion of purgatives, and particularly his long experience with the digestion of ruminants, Zuntz has naturally been led to the belief that the explanation is almost wholly due to that of the mechanical work of the digestive processes, although not to the absolute exclusion of other processes. On the other hand Rubner's experience maintains that there is a heat production per se, a "luxus" combustion that does no good, free heat unavailable to the cells, and without attempting to explain how this takes place, he terms this peculiar heat-producing property of the food its specific dynamic action. Finally there is the hitherto little recognized opinion expressed by Friedrich Müller[1] to the effect that there is absorbed out of the food certain substances which are carried by the blood to the cells and there stimulate the cells to a greater metabolic activity.

The first two of these views have provoked critical discussion on the part of both Zuntz and Rubner and many of their coworkers and former students for a good many years. The view of Friedrich Müller has, I believe, received less attention. This is perhaps not surprising in that Müller set forth his view in a somewhat inaccessible publication. Three years later Müller in v. Leyden's Handbuch did not emphasize the explanation on the basis of specific stimuli to katabolism, thus suggesting that Müller himself had not appreciated fully the significance of his earlier suggestion.

The evidence used for the evaluation in this paper of these several conceptions is based almost exclusively upon experiments made upon

men in the nutrition laboratory of the Carnegie Institution in Boston.

The hypothesis that the increase in metabolism following the ingestion of food was due to increased digestive work, peristaltic action, intestinal activity, etc., was apparently strongly substantiated by the experiments of Loewy in Zuntz's laboratory, in which the intense purgative action of sodium sulphate with its increased attendant peristaltic activity was studied with men. These experiments, which have been widely cited by the Zuntz school and others, apparently demonstrated that sodium sulphate, a nonoxidizable substance, provoked great peristalsis, which was accompanied by a greatly increased metabolism, as measured by the carbon dioxide output and oxygen intake.

To study the effect of the ingestion of a food or the effect of the ingestion of a purgative, it is first necessary to establish a base line in which the metabolism is determined under conditions which may be stated to be approximately normal and constant, and then, after superimposing the factor, if the measurements of metabolism made during the second period are to have any quantitative value, the fundamental assumption must be made that the basic metabolism would have remained the same during this period. Inasmuch as the basic metabolism is dependent to a very large part upon the muscular activity of the subject, it is essential that the muscular activity should remain constant throughout the whole experiment.

During the 30 years which have elapsed since Loewy's experiments the need for constant muscular activity throughout the entire experiment has attracted increasing attention with succeeding decades, until at the present date it may be safely stated that each gaseous metabolism experiment to be of value should consist of two parts, each of equal value and either of no value without the other, namely, a record of the chemical observations with regard to the oxygen consumption and carbon dioxide production on the one hand and a graphic record of the muscular activity accompanied by pulse and respiration rates of the subject or animal on the other. Under these circumstances, therefore, it can be laid down as a fundamental assumption that all factors affecting the measurement of the metabolism must be the same in both periods save the influence of the superimposed factor. When working with men they must have the same degree of muscular activity, they must be either asleep in both periods or awake in both periods, and obviously in judging of the value of a series of experiments that have been used to so strengthen the mechanical view of the importance of digestive work we must question as to whether or no in Loewy's experiments these factors were properly considered.

A repetition of these experiments with modern technique and with extreme caution and regard to the muscular activity in both periods led to a complete refutation of the views advocated by Loewy, namely, that the increased peristalsis as produced by sodium sulphate resulted in an increased metabolism, and although the amount of sodium sulphate ingested, as it was in Loewy's case, was of sufficient quantity to produce intense peristalsis, an irresistible desire to defecate, which ultimately concluded the experiment, yet even under these conditions there was no measurable increase in metabolism.

In the belief that when the intestine is full of partly digested food products and epithelial débris the amount of mechanical work thereby incurred might be greater than that involved in several powerful peristaltic waves, experiments were made in which relatively large amounts of agar-agar were ingested, thus producing a bulky, voluminous stool. The agar-agar being practically nonoxidizable, there was no great complication due to the combustion of carbohydrate from the agar-agar. With the agar-agar it is reasonable to assume that there must have been an extensive segmentation process as well as peristaltic waves. But even under these conditions in the ideally controlled experiments there was absolutely no increase in metalbolism. In so far, then, as the experiments on men show with controlled conditions, the work of peristalsis and probably of segmentation is not sufficient to be measured in the great daily energy transformation of the body. It is impossible to think of muscular activity of any kind taking place without some slight increased metabolism, but the amount involved in intestinal activity must be so small as to be entirely negligible in the extensive energy transformations for body maintenance.

In an uncompleted research carried out with Dr. Joseph H. Pratt we have been studying the influence of deficient pancreatic secretion and its resultant decreased absorption of protein and fat upon the total metabolism following the ingestion of food. Two dogs with atrophied pancreas were employed. The carbon dioxide excretion was determined first without food and then after the ingestion of 500 to 1,000 grams of meat. There was an increased metabolism, to be sure, but if the intestinal mechanical work was the greatest contribution to this increase, there should have been a very much greater metabolism, due to the fact that these dogs had deficient absorption, and there was a passage of a large mass of fecal material through the intestines, much larger than with normal dogs. While the series of experiments is not yet completed, the evidence all points strongly to the fact that not only is the increase in metabolism following meat feeding no greater than with normal dogs, but, as a matter of fact, there would seem to be a somewhat less increase in metabolism than with normal dogs. The experiments, however, are complicated by

the fact that the normal dogs remain somewhat more quietly than do the depancreatized dogs, since with the voluminous stools the latter must of necessity defecate several times in 24 hours, and this produces some discomfort and there is extraneous muscular activity. It is seen, however, that all the extraneous muscular activity incidental to defecation and moving about the cage tends to increase the total heat production of the depancreatized dogs above that of the normal dogs. As a matter of fact, even with this extraneous muscular activity, the total increased metabolism is not only no greater with the depancreatized dogs than the normal dogs, but apparently somewhat less.

The difficulties of computing the heat production from the carbon dioxide excretion in dogs with deficient pancreatic secretion are such as to make direct oxygen determinations desirable, and a research is now in progress with this in mind. All the evidence is, however, to the effect that the passage of a large amount of undigested food through the intestinal tract of the depancreatized dogs is not accompanied by an increased metabolism at all proportional to that found after the ingestion of a similar amount of food with normal dogs of the same size. Under these conditions, therefore, it seems that the mechanical theory of the increased heat production following the ingestion of food must in large part fall to the ground. That theoretically at least there should be an increase in metabolism with every muscle contraction no one can deny, but that this increased metabolism, i. e., from intestinal activity, can be sufficient when pooled with all the other body processes to play any important rôle in accounting for the increase in metabolism following the ingestion of food is highly improbable.

We must dissent from Rubner's view of a free heat liberation that does not benefit the cells, since it is a fact that experiments, both on dogs and on men, show that following the ingestion of food there is an increased muscle tonus, as indicated by the pulse rate and frequently by the respiration rate, showing that the animal is living on a higher metabolic plan than formerly. Even if all extraneous muscular activity is precluded by using trained subjects there is, following the ingestion of food, a great increase in the pulse rate and general muscular tonus, in other words one may say that internal muscular activity is considerably increased.

The increased heat is thus a product of cell action and the question as to its economic value acquires a new significance. A man asleep with lowest heat production is of little value to the world, awake with no external muscular activity he has increased internal activity and is capable of intellectual life. Sitting up, standing, working, all call for cumulative muscular or cellular activity, and hence the cells are increasingly used. Can we say that a cellular activity representing

the difference between asleep and awake is not of value? Similarly the increased tonus of the body following the ingestion of food may be of distinct economic value. Certainly there is increased cellular activity and the question as to the value of the increased heat becomes an economic as well as a physiologic one.

In judging of the physiological value of a moderately increased metabolism we must not overlook the fact that a temperature rise accompanies the increased metabolism. The stimulation of the respiratory center and the increase in extensibility of muscle by rise in body temperature are results worthy of serious thought. Furthermore Barcroft and King have demonstrated the increased dissociation of oxyhemoglobin by rise in temperature. They, as well as Pembrey, consider a moderate rise in temperature as distinctly beneficial to the body.

For a number of years, in conjunction with my associate, Mr. T. M. Carpenter, the influence of the ingestion of food on gross metabolism has been an object of experimental study. The earlier experiments were planned in that a subject should enter the respiration chamber after a given meal and there should be a study of the total metabolism, including the heat production and gaseous exchange, for four consecutive 2-hour periods. These experiments showed in common with those of all other observers that with the ingestion of practically all kinds of foodstuffs there was an increased metabolism, and that there were marked differences in the degree of intensity of metabolism, dependent upon the kind of foodstuffs. We found, as usual, the most prolonged rise to follow the ingestion of protein, but contrary to Zuntz, we found likewise great increases after the ingestion of carbohydrates. With the development of a special respiration apparatus, it became possible to study the effect of the influence of the ingestion of food in short periods, and since the research has been moved to the new laboratory in Boston, practically all of the experiments have been in connection with the small respiration apparatus, with which 15-minute experiments can be made rapidly succeeding each other and thus the qualitative changes in the intensity of the metabolism quickly noticed. Upon the ingestion of 100 grams of the various sugars, both mono and disaccharids, it was found that the several carbohydrates differed considerably in their effect upon metabolism. Thus dextrose showed the least action, there being but a slight increase in the oxygen consumption. On the other hand levulose, which is chemically so closely allied to dextrose, produced very much greater increase in metabolism. Cane sugar likewise stimulated metabolism greatly.

While the stimulation after the ingestion of protein was much greater than after the ingestion of carbohydrates, the body reacted much more quickly to carbohydrates than it did to protein.

Some recent experiences with diabetics and with normal individuals under conditions of acidosis lead strongly to the belief that the presence of acid stimulates metabolism enormously. In conjunction with Dr. Joslin we have found that diabetics when under conditions of severe acidosis have a much higher metabolism than when the acidosis is mild, and indeed, although we can at present state only that the high acidosis is coincidental with the high metabolism, it is probable that the high acidosis may be the primary cause of the high metabolism. Similarly with normal individuals, when subsisting upon a carbohydrate-free diet, there is developed an acidosis which results in a very highly increased metabolism. Singularly enough, normal individuals, and indeed diabetics, indicate a tendency toward a tolerance for the presence of these acids, inasmuch as the extremely high metabolism following the rapid onset of acidosis decreases somewhat as the acidosis continues, and with diabetics it is possible to have a very high percentage of β-oxybutyric acid in the urine with a metabolism although above normal, not proportionately as much above normal as would be expected from the amount of acid present. The great significance in this connection is the fact that the rapid withdrawal of carbohydrates from diabetics who have had free diet may produce an acidosis which is so severe as to lead into coma, although the actual amount of β-oxybutyric acid present in the body and excreted in the urine is by no means as great as in longer cases of diabetics who have become more tolerant to it.

Of particular interest is the experiment made with a severe diabetic in which after administration of 100 grams of levulose there was a noticeable increase in both carbon dioxide production and oxygen consumption, and singularly enough there was not the slightest alteration in the respiratory quotient, showing that the increased metabolism was due totally to a combustion of materials other than the ingested carbohydrates. The low respiratory quotient of 0.69 was maintained throughout the entire test, although the metabolism at times increased nearly 30 per cent of that before taking the sugar. Since throughout the whole period the subject, who was an ideal one, lay absolutely quiet without an extraneous muscular movement of any kind, it can be seen that the increase in metabolism could not be ascribed to external muscular activity.

These experiments, therefore, lead us to the belief that there are absorbed out of the food, substances which, carried by the blood, stimulate the cells to greater metabolic activity, and at this date, 13 years later than the original statement by Friedrich Müller, all we can add is that the substances absorbed are probably of an acid nature.

The amino acids of protein intermediary metabolism, the glycuronic and similar acids of the carbohydrate- and, indeed, protein- intermediary metabolism and the β-oxybutric acid of the intermediary fat metabolism, may each in proportion to the degree of formation stimulate the activity. Since experimental evidence is to the effect that the sugars react in increasing activity in the following order, dextrose, saccharose, and levulose, the asymmetric carbon atom, the ketone group, and the aldehyde group may each or all play a rôle in determining the degree of stimulation of the acid. The amount of experimental work suggested by these preliminary observations should lead ultimately to definite information regarding the molecular fragments in the foodstuffs responsible for the specific katabolic stimuli.

[1] Volkmann's Sammlung Klinischer Vorträge in 1900.

THE INFLUENCE OF FOODSTUFFS AND THEIR CLEAVAGE PRODUCTS UPON HEAT PRODUCTION.

By Dr. GRAHAM LUSK, Professor of Physiology, Cornell University Medical College, New York City.

Carl Voit believed that abundant food increased the power of the cells to metabolize materials brought to them. Zuntz has held that the work of the intestinal tract, or "Darmarbeit," was the real cause of the increase in metabolism after food ingestion. Voit took the ground that since the increase in metabolism, which followed the ingestion of meat in large quantity, was as great as that incident to the production of much mechanical energy, therefore "Darmarbeit" could not be the determining factor. Rubner has given many reasons against the view that intestinal work plays a considerable part in the increased metabolism after giving food, and Benedict has recently demonstrated that neither the production of diarrhea with saline cathartics, nor the intestinal work developed after giving non-absorbable agar-agar have any influence upon the heat production.

Rubner believes that there is a fixed requirement of energy necessary to maintain life. This quantity of energy may be furnished in the fasting organism by materials derived from the body itself. On giving food the foodstuffs are variously transformed with the evolution of heat until they are converted into materials which are available for use for the support of vital phenomena. These transformed materials may then be used in isodynamic replacement of the materials oxidized in fasting. The heat evolved in the production of these metabolizable compounds is added to the heat produced in support of the vital processes, and the total heat production is therefore raised above that of starvation.

The increase in heat production brought about by each foodstuff is different, and this power of each foodstuff is specific, hence Rubner has used the characterization, "specific dynamic action."

It may be further stated that Magnus-Levy remarked in an early paper that protein might act as a stimulus to metabolism, although he also added that there was nothing in his results to contradict the idea of Zuntz that intestinal work was the main cause of the increased heat production.

The construction of a respiration calorimeter by H. B. Williams which can measure the carbonic-acid outgo, the oxygen intake and the heat production of a sleeping or resting dog in hourly periods, has afforded the opportunity to uncover some new facts which throw new light upon the results heretofore obtained. These facts appear to demonstrate (1) that the increase in metabolism after protein ingestion is due to the stimulus of certain amino-acids acting on protoplasm and (2) that the increase in metabolism after giving sugar and fats is due to the increase of these metabolites in the blood stream.

The experiments were performed on quiet or sleeping dogs at an environmental temperature of 27°.

The subject of protein metabolism will be first considered. A dog whose basal metabolism was 22.3 calories per hour was given 1,200 grams of meat. During the second hour the heat production rose to 36 calories and during the third to 42. The heat production was maintained above 40 calories per hour through the tenth hour. From this point it gradually declined to 25 calories in the twenty-first hour. The increased metabolism was proportional to the increase of nitrogen elimination in the urine except during the second and third hours. In the second hour the metabolism rose almost to its maximum although the urinary nitrogen reached only a third of its maximum. Since the nonprotein respiratory quotient during this second hour was often above 0.9 it appears that carbohydrate and not additional protein was oxidized. On one day, when 700 grams of meat were given to the same dog, the specific dynamic action for the second hour calculated on the basis of the increase in the urinary nitrogen excretion was 139, and for the third hour it was 106. In other words the increase in the heat production of the time was greater than could have been derived from the extra metabolism of protein during these hours. These facts indicate that incoming amino-acids stimulate protoplasm to higher oxidation. This is more readily understood in the light of the recent experiments of Folin who has shown that if amino-acids are given they are absorbed and appear in the blood and muscle during the first hour after their administration, but that there is no urea formation until the second hour.

It was noted incidentally that after giving 1,200 grams of meat there was a large retention of carbon from the protein metabolized. The oxygen absorption of the period was such as to demonstrate that this carbon was retained in the form of dextrose. The production of dextrose from protein is therefore a normal function.

The next step was to give amino-acids themselves.

If Rubner's idea that protein could be of dynamic value to the organism only in so far as it was convertible into dextrose, be correct, then 25 grams of glycocoll or 20 grams of alanin which are completely convertible into 20 grams of dextrose in the phlorizinized dog should affect normal metabolism in the same way as do 20 grams of dextrose. If glutamic acid were given it might show a "specific dynamic action," for only three of its five carbon atoms are convertible into dextrose, while two on oxidation might yield free heat. Also tyrosin with its many cleavages before it reaches a stage for use by the cells might show a pronounced effect.

The amino-acids were given under definitely comparable conditions. It was found that a dog which received a standard diet at 6 p. m. produced 16.2 calories per hour between noon and 3 o'clock the next day. Giving a soup made with 2 grams of Liebig's extract of beef at noon did not change this result, although it is known that Liebig's extract powerfully stimulates the secretive activity of the gastric and pancreatic glands.

The various amino-acids were given with 2 grams of Liebig's extract at noon. Although 20 grams of glucose increased the metabolism only during the second hour, and only by 2.4 calories, showing a specific dynamic action of 3.2, it was found that 25 grams of glyocoll produced an effect lasting seven hours, caused an increased metabolism of 31.3 calories and showed a specific dynamic action of 70. That is to say, the extra heat production was equal to 70 per cent of the calories contained in the glycocoll ingested. The maximum increase in metabolism was reached as early as the second hour. During the first hour there was no increase in the urea elimination in the urine. The increase in the output of urea began in the second hour, but was the equivalent of only 0.7 calorie in terms of glycocoll metabolized, although the heat production during this hour rose 5 calories. During three hours the metabolism rose 15 calories, while the glycocoll metabolism could be estimated at only 3 calories, which was less than the increased heat production of the second hour alone. The metabolism of this same dog was uninfluenced after giving a solution of urea, hence the increase is not in any way due to the elimination of urea by the kidney. It was uninfluenced after the ingestion of 20 grams of glutamic acid although this was destroyed in the body as was evidenced by an increase in the amount of urea in the urine; hence the process of deamination is

not concerned in the increased heat production. Therefore since sugar and urea into which glycocoll is converted and the process of deamination by which this conversion is rendered possible have no influence upon the production of heat, and since amino-acids accumulate in the blood and tissue with little evidence of immediate metabolism, it seems necessary to conclude that the increased heat production which follows the ingestion of glycocoll is due to the fact that glycocoll itself acts as a stimulus to increased metabolism.

Alanin also acts strongly but not as powerfully as does glycocoll, while leucine and tyrosin show marked though smaller effects.

The action of glycocoll and alanin can not be due to sensory stimulation of the stomach, for a solution of urea which also may produce nausea has no effect on metabolism. In these experiments the dog betrayed no signs of nausea but remained in perfect quiet in the calorimeter.

A mixture made up of 5.5 grams of each of the five amino-acids, glycocoll, alanin, glutamic acid, leucin, and tyrosin, showed a more rapid absorption than when each was given alone and the effect on metabolism was as pronounced as that seen after giving 25 grams of glycocoll. It was greater than that following the ingestion of 100 grams of meat which contained about the same amount of nitrogen.

The work of Howland has shown that an infant 7 months old when given a modified milk administered in six equal portions during 24 hours and containing 3.58 grams of nitrogen per day produces during sleep 14.91 calories per hour. When 30 grams of casein were added to this diet and the nitrogen of the ingesta was 7.85 grams, the metabolism of the sleeping infant rose to 18.81 calories per hour, an increase of 3.9 calories or 26 per cent more than its former value. The casein added to the diet was the equivalent of 5.5 calories per hour. The increase in protein metabolism due to the high protein diet was the equivalent to 2.6 calories per hour. This increase in protein metabolism of 2.6 calories per hour brought about an increase of 3.9 calories in the metabolism of the sleeping infant. This is the only instance in which the total metabolism may be seen to be permanently raised above the calorific value of the extra protein metabolism. The explanation may lie in the fact that the youthful protoplasm is more sensitive to stimuli than that of the adult. In dog 1, the basal metabolism was 759 calories per square meter of surface in 24 hours, in dog 2 it was 784, in a dwarf 19 years old it was 775, whereas in sleeping infants of 3 and 7 months, it was about 1,100. These results could be obtained on account of comparable conditions of perfect rest.

As a conclusion, it may be stated that the increase in metabolism after the ingestion of meat is due to the mass action of amino-acids acting as stimuli upon the cellular protoplasm.

As regards the behavior of carbohydrate, the following results, obtained after giving 50 grams of dextrose in 150 cubic centimeters of water to the dog, may be considered typical. One hour after the ingestion of the dextrose the sugar content of the blood is found to be increased, but by the end of the second hour, and thereafter, it has returned to its normal percentage value. The volume of the blood, however, increases during the second hour, obviously in response to the osmotic pressure exerted by the increased sugar concentration. This increase in blood volume is demonstrated by a fall in the hemoglobin content of the blood. During the second to fourth hours after giving 50 grams of dextrose the metabolism shows an increase of 20 per cent above the normal basal value, the dextrose exerting a specific dynamic action of 4.8. During the fourth hour there is final absorption of all the dextrose ingested, the metabolism remains high, and the urine, which has been scanty, suddenly increases to 100 cubic centimeters. At the end of the same fourth hour the blood-sugar content is normal, indicating that during the withdrawal of water and the concentration of the blood the liver and muscles maintain the normal sugar content. During the second, third, and fourth hours the high metabolism is accompanied by respiratory quotients of about 1.00 (after allowing for the influence of protein metabolism). However, during the fifth hour, when the metabolism has returned to its basal value, a non-protein respiratory quotient of 0.83 indicates that a mixture of fat and carbohydrate is being oxidized. The glycogenic function enters into control, reduces the amount of carbohydrate available for combustion, and fat is oxidized as well.

It has also been shown that ingestion of 200 cubic centimeters of water, of 150 cubic centimeters of a 4.2 per cent solution of sodium chloride, or 150 cubic centimeters of an 8 per cent solution of urea have no influence upon the metabolism. It is therefore concluded that the high metabolism after giving dextrose is not due to osmotic changes between the blood and the tissues. The only remaining hypothesis which appears possible is that the increase in metabolism is due to the presence of a greater amount of free diffusible carbohydrate than was present before the ingestion of dextrose. It is known that the sugar of the blood behaves as if it existed in chemical combination (Loewi; Lépine). If this combining power over sugar remains constant, then when the blood is diluted, with coincident maintenance of the normal percentage content of dextrose, there would be an increased supply of free, readily oxidizable sugar molecules available for the nutrition of the cells. Hence carbohydrate alone is oxidized, and the metabolism rises in virtue of an increased supply of nutriment throughout the organism.

An emulsion of olive oil ingested by the dog caused an increase in metabolism, probably for similar reasons.

The experiments as to the behavior of dextrose confirm the work of Zuntz and of Rubner in many particulars, but they bring to light new points which show that the theories of both Zuntz and Rubner will have to be revised.

The views here expressed, however, conform to the "older" view of Carl Voit, who believed that the presence of abundant food increased the power of the cells to metabolize.

It was recognized by Rubner in his book[1] that when mixtures of foodstuffs were given the total heat production was not the sum of the increases which each foodstuff would have brought about had it been given alone, but was considerably less. Rubner explained this on the theory that the small amounts of protein which were ingested in the mixed diet merely replaced that metabolized in fasting, and therefore did not exert a specific dynamic action. He added that he did not deny the possibility of another explanation, it being conceivable that mixtures reacted specifically or that one material, to a certain extent, took over the function of another.

Although much work apparently confirms Rubner's first theory, yet certain facts here presented have established another point of view.

When dog 2, whose basal metabolism was 16.2 calories per hour, was given a mixed diet containing sufficient food to maintain the metabolism for 12 hours the heat production rose to 20.6 calories per hour during 6 hours. Addition of 20 grams of alanin to the diet caused no increase in the metabolism, although given alone it increased the heat production from 16.2 to 19.2 calories per hour. Alanin with the mixed diet exerted no specific dynamic action.

When 20 grams of glycocoll were added to the same mixed diet the heat production rose to 22.7 calories per hour, the same height to which 25 grams of glycocoll given alone will raise the metabolism. The addition of glycocoll to a mixed diet, therefore, does not raise the metabolism higher than glycocoll given alone would raise it. This affords the proof of a reciprocity in the action of glycocoll and the non-nitrogenous foodstuffs.

The explanation is the following: Amino acids act as stimuli upon the cells, raising their power to metabolize. They may act instead of nerve stimuli when increased heat production is required in the presence of external cold—the chemical regulation of temperature of Rubner. The energy liberated in response to these stimuli may be supplied by carbohydrate or fat. When fat and carbohydrate are given separately or together there may be an increased heat production on account of the increase in the quantity of ma-

terials available for the nutrition of the cells. With the cessation of absorption and the return of the blood to the composition it possessed before food was taken the metabolism falls to its basal value. The increased heat production after giving carbohydrate is accompanied by increased movement of the cell particles, for when the absorbed amino-acids are taken with carbohydrate they encounter a rhythm of cellular motion which they themselves might alone produce, but to which they can not further contribute.

These results establish a more exact conception of metabolism. One may conclude that there are the following forms of metabolism in the quiet or sleeping dog excluded from thermal influences: (1) A basal metabolism, in which the cells are nourished by a blood stream which does not receive food from the intestinal tract, but the composition of which is regulated by the organs of the body; (2) a metabolism due to plethora, induced by an increased quantity in the blood of carbohydrate or fat metabolites which are being absorbed from the intestine; and (3) a metabolism due to the stimulus of certain incoming amino-acids acting upon the cells. The metabolism of plethora and the metabolism of amino-acid stimulation can not be added to each other; there is no summation of effect when both influences are brought into action together. In other words, the rhythm of cellular motion induced by the presence of carbohydrate is not further intensified by the stimulus of amino-acids, unless the latter alone would accomplish the result.[2]

DISCUSSION.

KARL LANGENBECK, Boston: Nutrition, like other functions of the body, is rhythmic. It suggested itself to me three and a half years ago that some light might be thrown on metabolic processes, if the rhythm be accentuated by very gradually lengthening the nutrition interval, without allowing the body to lose weight.

Fourteen months ago, when I reached taking one meal every other day, there was a rapid fall from the regularly maintained average of 145 pounds to 137 pounds. In order not to interfere with the fasting interval, I took a lunch three hours before dinner, which checked the loss of weight and started a rise. In February last I reached a practice of eating every third day, which I have continued since, taking a substantial luncheon at 1 or 2 o'clock and dinner at 6; that is to say, food is taken only during 6 hours of the 72. The meals are hearty but not in excess of what a vigorous man would eat on such occasions daily. They little exceed three times the diminished diet recommended by Chittenden for daily consumption. The need for water during and immediately after meals is great. The average

weight has risen in the past 14 months to 154 pounds. The fluctuations are surprising, 150 pounds "Nüchtern-Gewicht," rising to 159–160 pounds an hour after dinner, when thirst has abated. One stool regularly and copious micturition on the morning after eating, when the weight falls to 156–157 pounds, continuing to do so regularly during the following two days of fast to 150 pounds.

The sudden increase of weight, strange to say, is not inconvenient or even felt, due mainly to absorption of a large amount of liquid into the cells, for blood and lymph alone would hardly stand this dilution. It is retained for 14 hours before the first water is passed.

The feature of thirst and sudden rise in weight has come gradually. Two years ago similar 2½-day fasts were taken weekly with fluctuations of about 3 pounds. It would seem as if there had come an increased absorptive capacity of the cells. At that time, after-resumption of eating, no increase of bodily temperature was obtruded on feeling; now, two hours after the second meal there is an intense sense of heat often with perspiration. These evidences of increasing metabolism were enforced by growing physical weakness, breathlessness after exercise, and need of rest, which came to a climax a year ago and then subsided and passed, except that rest of 12 hours' duration is still needed. The heat and unusual need for water when eating are, like the physical weakness, also passing phases, the former having come to a climax about April and May and being now much less. The water, about the same time, was largely passed the next morning. Now, it is held by the tissues noticeably longer, foreshadowing the time when it will be held by the restored protoplasm of the cells, so that unusual drinking at meals will not be a need and the excessive fluctuation in weight subside.

Not undertaken with a dietetic aim, but, quite the contrary, of studying a grossly exaggerated nutrition rhythm, the results promise to reconcile two opposing views; von Voit's, that nutrition takes place best under a generous diet and Chittenden's that one, little greater than the theoretical, in aggregate, works for physiological economy.

With an anemic person getting the system in balance involves time, rest, and severe stress. Increased sensibility and irritation come to a climax and subside with the physical prostration. This is not the occasion to speak of them.

When the system is again in balance a shorter nutrition rhythm will unquestionably be desirable.

WALTER MOORE COLEMAN, Washington: The position taken by Drs. Benedict and Lusk that increased metabolism is due to amino-acids is in line with my explanation of sleep as due to increase of carbonic and lactic acids in the blood. My curves of heart and lung action for

sleep, published in Berlin in 1909 by Mayer and Müller, show a break or lapse or lowering in respiration just before sleep. Thus results a slowed blood flow and want of oxygen in the brain, which diminishes the sensitiveness of the cerebral cells to messages from the outer world and lessens cerebral impulses to the muscles. Unconsciousness follows, while the increase in carbonic, lactic, and other acids in the blood from lessened oxygen is inciting the breathing center to deprive the cerebrum of its partial respiratory control which it held during waking; stinted and surplus breathing cease. The effect of these acids upon the activity of the cells in the spinal bulb is analogous to the increased cellular activity due to the presence of amino-acids after the ingestion of food. I believe that the conclusions of Drs. Benedict and Lusk will prove correct and the theory of Prof. Dr. Rübner incorrect. The position of Zuntz appears to be correct to a slight extent only.

Prof. LUSK: As regards Prof. von Noorden's view that the activity of the liver contributes largely to the specific dynamic action, the work of Folin should be recalled. This shows that ingested amino-acids accumulate in the blood and tissues and are not retained and modified by the liver. As regards Prof. Benedict's experiments on acidosis in diabetes, it has been shown in our laboratory that the metabolism in phlorhizin glycosuria may be increased 50 per cent above the basal value after three days' continuance of the glycosuria. During the first few hours after the drug is given the metabolism does not rise, so that sugar elimination by the kidney does not enter in as a factor. Older of our experiments lead also to the conclusion that the acidosis of phosphorus poisoning is accompanied by a largely increased heat production.

Dr. DIESING: Meines Erachtens ist bis jetzt eine Kraftquelle bei allen diesen höchst anerkennenswerten Versuchen, den Einfluss der eingeführten Nahrung auf den Stoff- und Kraftwechsel festzustellen; nämlich die Kräfte, die in Form von Licht in die Haut des Organismus eingestrahlt werden. Es ist Ihnen Allen bekannt, dass das in die Haut eingestrahlte Licht in der Haut Pigmente bildet, und es ist auch schon früher die Furcht angesprochen worden, dass diese Hautpigmente die Vorstufe des Haemoglobins darstellen. Auf diese weise ist die Verknüpfung der im Licht befindlichen Kraftquelle mit dem Stoff- und Kraftwechsel vorgestellt. Ich habe mich seit 1905 mit Versuchen in dieser Richtung beschäftigt, und habe nähere Anführungen über diese Hypothese und ihre praktische Verwertung in meinem 1908 erschienenen Büchlein "Das Licht als biologischer Faktor, eine Physiologie und Pathologie des Farbstoffwechsels." Ich möchte die Herren, die such mit diesen Versuchen beschäftigen, bitten, die Kraftquelle des Lichtes dabei in Betracht zu ziehen, und

bin uberzeugt, dass denn recht bedeutsame Resultate gezeitigt werden sein.

Prof. Dr. RUBNER: Ich habe Ihrer Versammlung mit grössten Interesse angewohnt, und freue mich, dass die Frage der "specific dynamic action" durch neue Untersuchungen weiter gefürht worden sind. Die Erklärungen der Thatsachen wechseln mit der Zeit: das ist die Geschichte der Wissenschaften. Ich freue mich constatieren zu können, dass meine alten Untersuchungen um endlich bestätigt worden sind.

[1] Die Gesetze des Energieverbrauchs, p. 410.

[2] The full details of this work are given in six papers on "Animal Calorimetry," Journal of Biological Chemistry, 1912, vols. 12 and 13.

TUESDAY AFTERNOON, SEPTEMBER 24, 1912.

AN ANATOMICAL ANALYSIS OF GROWTH.

Dr. HENRY H. DONALDSON, The Wistar Institute of Anatomy, Philadelphia, Pa.

It is my purpose to give an outline of the status of the work on the anatomical analysis of growth and to include a few results as illustrations.

Among the vertebrates sufficient data have been published to form satisfactory growth graphs for the entire animal between birth and maturity, or at least during the period of active growth, for the chick (Minot, 1908); rat, albino (Donaldson, 1906); rabbit (Minot, 1908); dog (Aron, 1911); guineapig (Minot, 1891); man (*a*) Caucasian (Roberts, 1878, and others); (*b*) Mongolian (Mishima, 1904).

For the graphs of fetal growth there are corresponding data for the rat (Stotsenburg MS.); rabbit (Fehling, 1877); pig (Lowrey, 1911); man, Caucasian (Jackson, 1909).

These results say nothing, however, about proportional changes within the growing body.

All students of growth have recognized the need for an analysis of the total growth into its components—as represented by the growth of the parts (systems) or organs of the body.

These data are hard to obtain and most of the earlier investigations on the anatomical analysis of growth are unfortunately fragmentary, whereby their usefulness is greatly impaired. Some of the more recent studies are, however, very instructive, although in none are the observations carried much beyond the active growing period.

Bearing on the growth of parts of the body, the most complete series of records of the weights of organs at different ages after birth have been made for the dogfish (Kellicott, 1908), age inferred from size; rat, albino (Jackson), according to age (MS.); (Hatai), age and size (MS.); rat, Norway (Hatai), age and size (MS.); man (Vierordt, 1890; composite).

For the fetal period there are the records for the pig (Lowrey, 1911); man (Jackson, 1909).

The data for the rat have not yet been published, while the other studies have been printed at intervals during the last four years.

All these series present frequent determinations extending over long fractions of the life span. The incomplete records, which are relatively very numerous, we pass by at this time.

Data of this sort have their uses: (*a*) For descriptive zoology, (*b*) for comparative anatomy.

Also as standards: (*c*) For measuring pathological deviations, (*d*) and degrees of physiological adaption, (*e*) also for the study of types of growth.

We find at once a ready application for these data in the development of the osseous system (skull), for example, under various protein diets, as used in the experiments of Mendel and Osborn, or types of diet as used by Chalmers Watson, 1907, 1908; while in our own laboratory, by the aid of these tables, it has been possible to study modifications in the viscera induced by domestication, inbreeding, hybridization, and exercise.

It is a familiar fact that the viscera form but a small fraction of the body weight, and that, therefore, in studying the growth of the entire animal, we are observing mainly those changes which occur in the other systems.

It is not easy to get a precise expression for the relative weight of the viscera, nor the change which this weight undergoes between birth (or the period of greatest visceral development) and maturity.

The following tables give a general idea of this relation, however.

Bischoff (1863) gives for man—

	Body eviscerated.	Viscera.	Visceral ratio.
	Per cent.	*Per cent.*	
Birth, 1 male, 1 female	62.5	37.5	2.3
Maturity, 1 male, 1 female	83.8	16.2	1

Vierordt (1890) gives—

	Body eviscerated.	Viscera.	Visceral ratio.
	Per cent.	*Per cent.*	
Birth	76.6	23.4	2.4
Maturity	90.2	9.8	1

Lowrey (1911) gives for the pig—

	Body eviscerated.	Viscera.	Visceral ratio.
	Per cent.	*Per cent.*	
Birth	84	16	2
Maturity	92	7.8	1

In the albino rat the maximum relative weight of the viscera is found, not at birth but at from three to five weeks of age. Jackson (1912) gives—

	Body eviscerated.	Viscera.	Visceral ratio.
	Per cent.	*Per cent.*	
Birth	82	18	.....
3 weeks	78.7	21.3	1.6
1 year	86.7	13.3	1

Hatai (MS.) gives for the albino rat—

	Body eviscerated.	Viscera.	Visceral ratio.
	Per cent.	*Per cent.*	
Birth	84	16	.....
5 weeks (50 grams)	77.9	22.1	2
Adult (200 grams)	85.3	14.7	.....
Adult (400 grams)	88.8	11.2	1

However the important point brought out by a study of these relations in man, the pig, and the albino rat is that the proportional value of the viscera is about twice as great at the time of their best development as it is at maturity.

We may fairly assume that this is a significant change.

Turning to the analysis of the growth of the albino rat in terms of divisions of the body, Jackson (1912) has in press a study (based on age) of the growth of the head, trunk, fore limbs, and hind limbs, and also a study of the growth of the musculature, skeleton, skin, and the viscera, taken as a whole. (Thoracic and abdominal viscera and central nervous system.)

Jackson here shows that from birth onward the incidence of most active growth passes like a wave from the head and upper limbs to the lower limbs and the trunk, the high relative weight for which is last attained.

The same relations are probably true for man.

Passing to the several viscera, both Hatai and Jackson have studied the weights of the organs in relation to the body in the case of the albino rat, and it is these observations (especially as made by Hatai, with whose work I am more familiar) that I desire to present in some detail.

The organs of the albino rat weighed in these studies were the brain, spinal cord, eyes, lungs, heart, kidneys, liver, alimentary tract, spleen, testes, ovaries, thyroid, thymus, suprarenals, and hypophysis. All the weighings were on fresh material.

I call attention first to the two size groups into which the organs fall—the liver and alimentary tract forming the great mass of material and constituting one group, while the remaining viscera are small and make a second group by themselves.

Dr. Hatai has called attention to the fact that the graphs for growth representing the viscera may be divided into three types:

Type 1 is that of the nervous system, best represented by the brain, in which very rapid growth occurs early, followed by a long period of very slow growth, the chief characteristic of this type.

Type 2 is that of the testes, which shows a sinuous graph, the appearance of the delayed function here being accompanied by an accelerated growth. This type of graph also represents the growth of the ovaries, so that it is characteristic of the gonads in general.

Type 3 is the approximately straight-line graph. This type applies to all the other viscera. These, with some slight exceptions, establish a constant rate shortly after birth, whereby a given increase in the weight of the entire animal is accompanied by a given increase in the weight of the viscus. Wherever there is a deviation it is represented by a slowing in the relative growth of the viscus. The growth of the heart is the best example of this type.

The data from these graphs are based on 437 male individuals (268 Hatai, 169 Jackson male[1]), and 200 (Hatai and Jackson together) female. The data have been treated by approved statistical methods, and formulas for the several graphs have been obtained by Dr. Hatai.

So far as the three types are concerned, it is of interest to note that similar types have been found for the corresponding organs in the dog fish by Kellicott (1908).

The changes in weight for the three ductless glands—the thyroid, hypophysis, and suprarenals—are of the straight-line type. The relative growth is, in all three, similar to that of the heart.

In the albino rat the thyroid shows no variation according to sex; but in the case of the hypophysis and the suprarenals there is a marked sex difference, both these glands being much heavier in the female.

I am not aware that the sex relations of these two glands have been thus clearly established in any other animal, although there are incidental statements concerning all of them for man. These data enable us to show further that this is not the only interesting relation exhibited by these ductless glands.

The albino is a variety of the wild Norway rat (*Mus norvegicus*), but it lives always under conditions of domestication. Dr. Hatai has a long series of observations on the weight of the viscera in the wild Norway.

The weight of the total viscera in the Norways is a trifle higher than in the albinos; but when particular viscera are compared there

appear characteristic differences in opposite directions. Norways have heavy brain, spinal cord, and spleen, light heart and kidneys. The deviations of the albino are not due to albinism as such. Apparently they arise in response to the complex conditions represented by domestication. This same influence, domestication, seems to be the cause of the differences found between the suprarenals and the hypophysis in the albino, as compared with the Norway rat.

Dr. Hatai's weighings show that the hypophysis in the Norway rat is notably smaller than in the albino, the sex differences remaining the same.

On the contrary, the suprarenals are larger in the wild Norway than in the albino, being about twice the size. The sex difference also remains the same.

Chalmers Watson (1907, 1908) has already pointed out this difference in weight and referred it to domestication, but he did not distinguish the sexes in his tables.

The proportions from Hatai's series are:

	Body weight.	Hypophysis.	Suprarenals.	No.
Norway:				
Male	223.4	0.0071	.0746	14
Female	225.1	.0085	.1237	15
Albino:				
Male	.....	.0081	.0358	....
Female	.....	.0183	.0589	....

Average difference: Hypophysis, Norway, 75 per cent of albino; suprarenals, Norway, 209 per cent of albino.

If it should appear that similar changes took place under domestication in other mammals we would have one more important instance of adaptation within the organism to changes in the environment.

Generalizations as to the relative importance of the various organs, and especially the significance of the variations in the different ductless glands, must await collection of data on a series of forms, though it seems highly probable that other mammals will be found similar to the rat in these various characters and in their power of physiological adaptation. The illustrations of the utility of these data on the weights of organs are then the clear distinction in the weight of the ductless glands, the suprarenals and hypophysis, according to sex, and their change in weight in the Albino as compared with the wild Norway, probably the result of domestication. Other examples could be given, but these must serve for this occasion.

It has been the purpose of this report to call attention especially to the considerable series of data which apply to the growth and weight relations of the various organs of the Albino rat and its wild

ancestor, the Norway rat, as these data now furnish reference tables by which changes in both forms of this animal under various experimental conditions can be advantageously studied.

[1] Excluding birth records.

NUTRITION OF THE EMBRYO.

Dr. JOHN R. MURLIN, assistant professor of physiology, Cornell University Medical College, New York City.

A. THE MECHANISM OF NUTRITION.

Only a few years ago the mammalian ovum was regarded as nothing more than a maternal cell, just as much at the mercy of the maternal circulation for its nourishment as any other cell of the body, and the provisions made after fertilization for insuring its supply of maternal blood were looked upon as beneficent, not to say providential, adaptations for the special care of the offspring. Partly through the biological observations of Häcker, Boveri, and Beard, who have demonstrated the independence of the "Keimbahn," or germinal path, and partly by the embryological studies of Hubrecht, Assheton, v. Spee, Peters, and others, who have directed attention to the details of the process of implantation of the ovum in the wall of the uterus, it has gradually dawned upon us that the ovum is already, to a large degree, an independent organism, capable, even in the face of difficulties, of looking out for its own nourishment at every step of its development. In fact, the only possible interpretation of events in the ovary, previous to the liberation of the ovum, is that a certain cell is selected to grow and thrive at the expense of its fellows, because (according to Miss Lane-Claypon, quite fortuitously; according to John Beard, by prearrangement) it possesses the mechanism which enables it to appropriate to its own purposes the materials contributed by its less fortunate neighbors.

Set free from the ovary, the mammalian ovum possesses only a small amount of deutoplasm, but it carries with it a fringe of follicle cells on which it feeds in its progress down the Fallopian tube. The tube itself supplies something in the form of a jellylike layer of albuminous material, secreted in response to the presence of the ovum, which is in all essential respects the analogue of the white of the hen's egg. In some mammals, like the rabbit, it has been ascertained by Assheton that the ovum feeds upon this albuminous secretion, formed in part by the uterus as well as the oviduct, for nearly a week after fertilization, and that only when this supply is exhausted does it begin to burrow into the uterine mucosa for more nourishment.

From the histological studies recently made on an age series of hedgehog embryos by Hubrecht, and on very early human ova by Bryce and Teacher, and still later by Young, of Edinburgh, it is clear that the process of implantation, from the standpoint of the embryo, is a continuation of the process of proteolytic digestion by which the albuminous secretion of the tube and uterus was made available. The ectodermal cells which mediate this function are known collectively, after Hubrecht, as the trophoblast. Although an enzyme has not been demonstrated by chemical means in these earliest stages, it has been found recently as early as the second month by Gräfenburg, and there can be no doubt, from the histological picture, that a very active one is at work, or that it is produced by these trophoblastic cells. Whatever they touch, according to v. Spee, undergoes solution. Wherever the ovum happens to touch the uterine wall after the fringe of follicle cells is digested away, the ovum adheres to it and soon dissolves a depression; this depression becomes a cavity and the cavity extends as the trophoblastic cells increase in number. From the standpoint of the maternal body, implantation and placentation, according to Webster, Bryce and Teacher, and Young, represent an effort on the part of the organism to limit the invader and to restrict the effects of its enzymes.

By the time a circulation is necessary to distribute the proteolytic products to all the embryonic cells, a circulation is necessary also (it is easy to fall into teleological language because of our ignorance of the mechanism by which blood vessels are produced) to connect the embryo with its food supply, and we have the first steps in the formation of the true placenta.

The question whether the placenta, when fully formed, is an organ of digestion for the fetus, or whether it is merely a structure for diffusion of food materials already in solution, is one which has been actively though intermittently discussed since the time of Harvey. Harvey himself expressed the opinion in 1651 that the placenta makes the material brought to the fetus available "by a sort of digestion." But evidence of this which would be incontrovertible has been slow in accumulating. The histological evidence of a proteolysis effected by the early trophoblast, which has just been referred to, creates, now that we have it, a strong presumption that the cells derived from the trophoblast will continue to exercise similar functions. Such enzymes have, in fact, been extracted from the true placenta by Ascoli, Merletti, Bergell and Liepmann, and Savaré.

Recently, Gräfenburg has investigated human placentas of all ages from two months to the end of gestation and has found a tryptic enzyme clearly demonstrable by Muller and Jochmann's method only up to the end of the fourth month. Gräfenburg states that the cells of Langhan's layer begin to break up and to disappear about this

time, and he reasons that therefore they must be responsible for the production of the enzyme. . Products of proteolysis, especially albumoses, have, however, been found by Mathes, Basso, and Hofbauer both in the fresh placenta and in minced placenta after undergoing autolysis at all stages of gestation; but amino acids are not found except after prolonged autolysis or after prolonged digestion of protein by means of placental extracts. Hofbauer concludes from his studies that proteolysis in the placenta normally stops at the albumose stage and that synthesis takes place immediately the trophoblastic cells have been passed. That the fetal proteins differ from the maternal and that a resolution and resynthesis is therefore necessary, Hofbauer infers from such facts as the following: A difference in the content of euglobulin in fetal and in maternal blood, demonstrated by Joachim; the presence of amboceptors in maternal blood which can not be found in fetal blood, a fact brought to light by Polano, and the demonstration by Braus of a chemical body, which produces a precipitin with the serum of rabbit's blood, present in the maternal body of *Bombinator pachypus*, but not present in the fetus of the same species.

The discovery, reported within the year by Abderhalden and Kiutsi, of enzymes present in the blood of pregnant subjects, which are capable of digesting placenta peptone, is probably to be interpreted as another evidence of the difference between maternal and fetal proteins; for the authors state that its nature is that of a protecting enzyme intended to destroy proteins of fetal origin.

It seems possible that certain albumins can pass from mother to fetus entirely unchanged, for precipitin reactions have been obtained in fetal blood by both Ascoli and Lochhead after parenteral injection of egg white into the pregnant guinea pig, and yet it must not be forgotten that Friedemann has shown that cleavage products of certain proteins give the same precipitin reactions as do the native proteins. Hence, it is by no means clear that these precipitins in the fetal blood were not produced by albumoses or peptones of the egg albumin formed in the placenta. At all events, the evidence is now quite sufficient to state with some positiveness that, in the early months of pregnancy at least, the trophoblastic cells make it their business to modify all the protein which normally passes from mother to fetus. That some fetal organ takes over this function after the disappearance of Langhans's cells is proved by the fact, on the one hand, that the syncytium becomes extremely thin late in pregnancy; and by the fact, on the other hand, that the fetus, if prematurely born, is able to live without this work of intervention on the part of the placenta. Mendel and Mitchell, in their chemical studies on growth, reported some five years ago, state that the pro-

teolytic enzymes, like the glands which elaborate them, come into evidence at a comparatively late period of embryonic life. Pepsin was found by Toldt in the gastric mucosa at the end of the sixth month. Mendel and Mitchell were able to demonstrate the presence of the deamidizing enzymes, adenase, and guanase in embryo pigs, the former in the liver as early as the forty-fourth day, the latter in other viscera at about the middle (sixty-second day) of embryonic life.

So much for the mechanism by which the embryo obtains its most essential building material, the proteins.

We naturally expect that other organic foods must likewise undergo a process of naturalization at the line which separates maternal from fetal structures. For the fats, Hofbauer has found the same histological picture in the trophoblastic cells as is always found in the epithelium of the intestinal villi in active absorption of fat. Thiemich was unable to influence the composition of fetal fat by feeding a pregnant dog with palmin and linseed oil, and Oshima finds that the number of fat granules in the fetal blood in no way corresponds to the amount of fat in the maternal circulation. Hofbauer completes the indirect evidence for a transformation of fat by showing that a fatty acid (laurinic acid), characteristic of coconut oil, can be demonstrated in the fetus when the oil is fed to the mother. While a lipolytic enzyme has not yet been found in the placenta, it seems clear that neutral fat can not pass the trophoblast without cleavage into fatty acid and glycerin.

For the transformation of carbohydrates, amylolytic, and glycogen-splitting enzymes have been found in the placenta, the former by Charrin and Goupil, Bergell and Liepmann, and by Lochhead and Cramer; the latter by Merletti, Bergell and Liepmann, Lochhead and Cramer, and Hofbauer. Even glucose, it is said, can not pass the trophoblast by simple diffusion, but is dependent upon a selective activity of the trophoblastic cells (Merletti). Laevulose is found in the fetal blood.

The older view, maintained by Bernard and by Pflüger, that embryonic tissue is especially rich in glycogen has been definitely disproved within recent years by Adamoff, Mendel and Laevenworth, and Lochhead and Cramer. The last-named authors have made a study of the glycogen content of the placenta, the fetal liver, and the remainder of the embryonic body in an age series of rabbit embryos, and have noted a "distinct parallelism between the growth of the fetus and the amount of glycogen it contains."

In the earlier stages of intrauterine life of the rabbit the fetal liver lacks the power to store glycogen, and this power it does not acquire to any degree until the last week(1–4) of gestation. Up to this time the maternal side of the placenta "vicariously fulfills the

hepatic function as far as glycogen is concerned." Then, as the fetal liver develops its glycogen-storing capacity, the placenta loses it. The glycogen stored in the placenta and later in the fetal liver and other organs, besides representing an excess of carbohydrate, just as it does in the nutrition of the adult, may, as Lochhead and Cramer have pointed out, be of special significance in the production of mucin which has a carbohydrate radical and which is present in large quantity in all embryonic tissue.

Another factor of great importance in the nutrition of the embryo is the supply of iron for the production of its respiratory pigment. For the chick we know that the supply of iron is already present in the yolk of the egg, and the formation of blood corpuscles, with their content of hemoglobin, can be very satisfactorily traced by histological methods. The mammalian ovum, however, contains no iron for the manufacture of its respiratory pigment; hence, this constituent must be obtained from the mother. There are two possible sources: (1) The hemoglobin of the maternal blood and (2) the nucleo-protein of the food. Concerning the transformations of the latter as a source of iron, we know next to nothing; hence, remarks may be confined entirely to the derivation of iron from the hemoglobin of the mother. How is this supply made available? Marshall has shown that, in the sheep, the blood which is extravasated in menstruation, but which, in this animal, does not reach the exterior, is decomposed, later is ingested by leucocytes in which iron can be demonstrated by microchemical methods, and, finally, in the event of conception, becomes a constituent part of the uterine milk or embryotrophe. After the formation of the placenta, the extravasation of a greater or less amount of blood as a constituent part of the uterine milk has been demonstrated for a number of ruminant animals (sheep, cow, deer, etc.), and following its ingestion by the amaeboid activity of the trophoblastic cells, various pigments found in the placenta, but not found in the virgin uterus, have been proved by both histological and spectroscopic methods to be derivatives of the hemoglobin.

According to the latest histological evidence furnished by Bryce and Teacher, the early human trophoblast does not ingest red blood corpuscles as such, but, according to Hofbauer, there can be no doubt of the presence of iron-containing compounds in the villi immediately adjoining the blood sinuses. There is scarcely any doubt that their source is the maternal blood filling the sinuses.

The iron-containing fraction of the destroyed hemoglobin is supposed to be transported directly by the fetal blood to the fetal liver, where certainly iron is stored as a compensation, according to Bunge, for the lack of iron in the milk. Points which remain to be cleared up are, whether the iron delivered to the placenta undergoes further

chemical change on its way to the liver, and whether it is deposited at once in blood-forming cells of the liver. (The reader is referred to Lochhead's excellent chapter on "Fetal Nutrition" in Marshall's "Physiology of Reproduction" for a fuller discussion of topics treated in the first half of the present paper.)

B. QUANTITATIVE RELATIONSHIPS IN THE NUTRITION OF THE EMBRYO.

The possession by the embryo from its earliest stages of a mechanism necessary to acquire, digest and assimilate its own building material and energy-producing materials supports the view, so often expressed on other grounds, of a parasitic relationship to the mother. There are, however, certain facts which have come to light in recent biochemical studies of the subject which permit of a different interpretation.

There can be no doubt that so long as the trophoblastic cells are able to establish the proper anatomical and physiological relationship to the maternal blood stream, the embryo relentlessly draws upon the circulation for materials to satisfy the cravings of its multiplying and developing cells. The problem of proper nutrition of the embryo, then, is properly to nourish the mother—to replace, by way of her own alimentary system, the materials drawn from her circulation, so that it may not be necessary at any moment to replace them from her own tissues.

(1) *Requirement for protein.*—In order to determine the total amount of materials required for the formation of a fully developed child at term, we have only to analyze the body of such a child stillborn, as has been done by Michel, Fehling, and others. But the practical question is not how much protein, fat, carbohydrate, iron, calcium, etc., does the newborn child contain, but how much of the various food materials must be placed to the credit of the pregnant mother at successive stages of the period of gestation to enable her to set up a branch establishment complete in all physiological and anatomical details and, therefore, capable of complete autonomy, without depletion of her own capital resources.

Does the pregnant organism exhibit any special economy for accomplishing this end? The earliest students of the nutritional balance sheets thought it did. Repreff, for example, finding less nitrogen in the urine of pregnant animals than in that of nonpregnant animals on the same diet, concluded that the katabolic processes of the mother's body must be reduced in order to permit the fetus to make use of the protein materials for growth. Hagemann, from experiments on dogs, and Ver Ecke, from experiments on rabbits, reached an exactly opposite conclusion. Analyzing the bodies of the newborn animals and the accessory structures (afterbirth, membranes, amniotic fluids, etc.) at birth and comparing the sum total with the amount of materials retained by the mother's body during

the entire gestation period, they found a net loss. Some of the materials must have come from the maternal body. As Ver Ecke put it, "Gestation constitutes a sacrifice of the individual for the good of the species." It appears, however, from more recent and better controlled experiments by Jägerroos, Bar and Daunay, and by the writer, that this view is extreme. Each of the last-named observers has had dogs come through the gestation period with a net gain rather than a net loss of protein. But this is not the whole truth. The early part of gestation in the dog, at least, is characterized by a tendency to nitrogen loss on the part of the mother. The period of this loss, according to Bar, practically coincides with the period of morning sickness in women, and has been interpreted to mean that the maternal organism has not yet succeeded in fully protecting itself against the action of the trophoblastic enzymes. With the completion of the placenta about the end of the fourth week in the dog, or the fourth month in the human pregnancy, the enzymes are thenceforth restricted in their action to the materials supplied by the blood and the period of nitrogen loss changes to a period of nitrogen gain. Under normal conditions, the nitrogen gain much more than compensates for the previous loss.

Two years ago Hoffström reported from Helsingfors complete balance sheets for nitrogen, sulphur, phosphorus, calcium, and magnesium from the seventeenth week to the end of gestation on a single case of human pregnancy. He found, in respect to all of these substances, that more was retained at the end of each week than could have been required, according to the analyses of Michel and Fehling, for the growth of fetus, membranes, and afterbirth. Bar and Daunay had already reported the same as regards nitrogen for the very last weeks of pregnancy in women. The conclusion, from both researches, is that in normally nourished pregnant women not only is the maternal body capable of meeting the demands of the fetus without loss, but that for each of the elements investigated there is a considerable gain on the part of the maternal body. For this reason, Bar speaks of the nutritional relationship between mother and fetus, not as a parasitism, but as an "harmonious symbiosis," meaning, by this, that each organism derives a distinct nutritional advantage from the partnership. Many different organs of the mother share in this advantage—the muscles, especially of the pelvis and abdomen, the subcutaneous deposits of fat, and the mammary glands, most conspicuously. Just how the presence of the fetus stimulates the maternal tissues to increased anabolic activity is not fully understood, the positive results of Starling and Claypon on the hormone action of fetal extract on the mammary glands not having as yet been fully confirmed.

Hoffström's paper contains curves which show the amounts of nitrogen, phosphorous, calcium, etc., which, on a known diet containing on the average 80 grams protein, 123 grams fat, and 196 grams carbohydrate in 24 hours, were utilized for the fetus and how much was retained by the maternal body itself.

2. *Requirements of the embryo for energy.*—Harbored as it is amongst the warmest organs of the mother's body, the fetus might be supposed to produce very little heat on its own account. It has been clearly demonstrated, however, that oxidation takes place in the fetal tissues as soon as a circulation is established, and we must suppose that it begins even before this. Two questions naturally arise, What foodstuffs furnish the potential energy required in the fetal tissues; and how much energy is required in comparison with the adult tissues?

No perfectly satisfactory determinations of the respiratory quotients which would enable us to decide what foodstuffs are burned in the embryo have yet been made. Those of Cohnstein and Zuntz on the sheep, published in 1884, were certainly faulty as to technique, and those of Bohr on the guinea pig (1900) are open to grave objection as to certain experimental conditions. The indications from both sets of observations are that carbohydrate furnishes the energy of combustion, and this is supported by some observations by the writer on newborn dogs. They are in disagreement, however, with experiments by Babak and by Scherer on newborn children where low respiratory quotients, indicating the combustion of fat, were obtained as early as one hour after birth. Experiments on animals, in which the O_2 and CO_2 tension in the blood of the umbilical vein and artery may be determined by the improved methods of Haldane, Barcroft, or Krogh, should clear up this problem in a comparatively short time.

The answer to the other question is more definite. Experiments by the writer on pregnant dogs have shown that the extra metabolism due to pregnancy is proportional to the weight of the newborn delivered, and is about the same per unit of surface (calculating this from the known weight curve of the embryo) as in the adult dog. Assuming that the accessory structures take little part, this makes the total metabolism per unit of weight of the embryos three days before birth equal to three times the metabolism of the mother dog. In the last two weeks of human pregnancy, as Carpenter and Murlin have shown, the total metabolism per unit of weight is but 4 per cent higher than in the nonpregnant woman under the same conditions. The small amount of this increase is due to the fact that the weight of the fetus is small compared with that of the mother and to the fact that a considerable part of the increased weight in pregnancy takes no part in the metabolism. Nevertheless the children born from these pregnancies in the first two weeks of their lives showed, while

sleeping quietly beside their mothers, a metabolism per unit of weight two and one-half times that of their mothers.

The explanation of this higher metabolism per unit of weight, in the opinion of the writer, we owe entirely to Rubner's law of skin surface. The embryo, like the infant, has, in proportion to its weight, a much larger body surface through which heat can be radiated. Reckoned on the basis of surface area, there is no evidence, as yet, that the metabolism either of the embryo or of the newborn is higher than that of the adult.

Summarizing the knowledge of to-day regarding the nutrition of the embryo, we may say: (1) That the embryo is provided from the first with a mechanism which enables it to digest and assimilate the materials of its immediate environment. The mechanism of digestion is located in the early trophoblast and later in the placental structures derived from this. These structures continue to discharge the alimentary functions, digestion, absorption, storage of reserve materials, etc., until the fetal organs are themselves developed far enough to discharge them. There is then a gradual shifting of the functions to the alimentary canal until, just before birth, it may be assumed that the proper organs are supplied with a complete complement of alimentary enzymes ready to attack the materials synthetized by the mammary glands. (2) The amount of protein material actually required for the growth of the embryo of any species can be determined only by analyzing an age series of embryos for nitrogen. A curve constructed from such data, when compared with a curve expressing the amount of nitrogen retained by the maternal body during gestation, shows that, under normal conditions, there is always an excess of available building material. There is, therefore, no necessity, from the chemical point of view, of a sacrifice of the individual for the good of the species, so far as gestation is concerned. (3) We do not know with certainty what materials are burned for the maintenance of its body temperature in the embryo, though the indications are that the most diffusible foodstuff, namely, carbohydrate, furnishes the bulk of the energy. As regards the intensity of the metabolism and, therefore, the total requirements for energy, the weight of evidence is that no more potential energy is required than for the newborn kept warm in bed beside its mother, and the latter amount is certainly not greater per unit of surface area than in the adult. Reckoning all the extra metabolism of the pregnant dog as belonging to the embryo alone, the amount per unit of weight three days before birth is about three times that of the mother dog. The metabolism of the newborn child, asleep beside its mother, is two and a half times the resting metabolism, per unit of weight, of the mother.

THE NUTRITION AND GROWTH OF BONE.

Dr. FRANCIS H. MCCRUDDEN, chemist at the hospital of the Rockefeller Institute for Medical Research, New York City.

This subject of bone growth is a very important one, to which very little attention has been given. When we remember that in all the various chronic rheumatisms, osteomalacia, rickets, osteitis deformans, osteoporosis, fractures, dwarfism, and faulty development bone growth is involved, we see the importance of knowing the normal. And yet almost no one seems to have made an experimental investigation of the question of normal bone growth. Bone is generally considered a dead tissue, not undergoing metabolism once it is laid down. Only Cohnheim and Adami definitely face the question and express the opinion that bone does undergo a continuous process of absorption and resorption, and even with these two pathologists it is merely an opinion and not based on any definite experimental studies. Several years ago, while making chemical studies in various bone diseases, I began to study osteomalacia, and my findings threw some light on this whole question. I shall therefore approach the subject in this discussion as I did in my work—through osteomalacia.

In osteomalacia the bones are soft and poor in lime salts like bones which have been decalcified *in vitro* by the action of acid, and so the assumption was naturally made that the decalcification in this disease is also due to the action of acid.

Chemical analysis of bone in osteomalacia shows that it contains more magnesium phosphate than normal bone,[1] a fact that at once excludes the acid hypothesis, for magnesium phosphate is more readily soluble in acid than calcium phosphate, and the content of bone in magnesium phosphate would therefore decrease more rapidly than that of calcium phosphate under the influence of acid. Chemical analysis, furthermore, brings out another point, namely, that the increase in magnesium and in osteoid tissue is not only a relative increase, such as one would expect if a certain quantity of calcium were removed, but an absolute increase leading to the conclusion that there is an apposition of new osteoid tissue poorer in calcium, but richer in magnesium salts than normally. The process, then, in osteomalacia is not a mere passive dissolving out of calcium salts. Old bone is being destroyed and new bone laid down, but the new bone is poorer in calcium salts but richer in osteoid tissue and in magnesium salts than normally.

Metabolism observations, too, are in accord with the conception of osteomalacia already outlined.[2] Complete balance studies, in which various elements in the food, urine, and feces were studied in the active stage of osteomalacia, have shown a loss of calcium and a

retention of magnesium and of sulphur, the latter an important constituent of the ground substance of bone.

Histological evidence throws but little light on the question of the nature of the process in osteomalacia, but it is of interest to note that osteoblasts—evidence of newly formed bone—are found in abundance in the region of the uncalcified bone. And this is in accord with the conception of this bone as new lime-free bone and not old decalcified bone.

All the evidence on the subject is against the acid theory. The body has an enormous power of neutralizing acid, so that any formed is at once neutralized and does not circulate. Attempts to produce osteomalacia artificially by the feeding of large quantities of acid have invariably failed and in diabetic acidosis, the condition in which the neutralizing power of the body is most severely taxed, there is no evidence of osteomalacia; furthermore, we have evidence that there is no great increase in acid formation in osteomalacia.

All the evidence, in fact, indicates that bony tissue, like other tissue, is undergoing a continuous process of breaking down and new formation. There is chemical evidence of building up or anabolic processes in bone during formation and calcification of the callus formed following a fracture, and during starvation catabolic or breaking-down processes come into evidence. The mineral salts excreted during starvation are much greater than can be accounted for by the quantities in the muscle or other soft tissue being destroyed, as measured by nitrogen excretion, and can only be accounted for by assuming a catabolism of bone; and analyses of the bones of starving animals show that they do, in fact, lose both mineral salts and organic matter and, in fact, in about the same proportions. Indeed, in the experiments of one investigator it was shown that this loss might be as high as 1 per cent per day of the total bone. We have histological evidence of this in the arrangement of the lamellæ. These are laid down along the lines of strain, but in the different periods of life the load to be borne and the direction of strain varies and the old lamellæ become absorbed and replaced by new; they can be seen to be undergoing absorption along one aspect, while new material is deposited on the other, so that the position of the individual lamellæ becomes shifted. Furthermore, the fact that rickets and osteomalacia can be produced in animals by withdrawing lime salts from the food is in accord with the conception of bone as a tissue which is continuously being destroyed and in need of new material to replace the old.

As a matter of fact, the conception of bone as a dead tissue not undergoing metabolism is a last remainder of the old view long since discarded that there is some subtle difference between the dead or

mineral elements and the living or organic elements, whereby the latter can take an active part in life processes, the former not. That the so-called inorganic elements do take a very active part in living processes is brought out by such work as that of Loeb and others. We all agree that the calcium, magnesium, and iron salts in the muscles and blood undergo metabolism and have to be renewed. If, then, the few per cent of these elements in the soft tissues are in a state of flux, why not also the many per cent in the hard tissues? The soft osteoid tissue in osteomalacia is to be considered, then, not as old bony tissue from which the salts have been dissolved out, but as new bone poor in lime salts, laid down to replace the old bone.

Having satisfied myself as to the nature of the process, I next inquired as to the cause. Why is bone abnormally poor in calcium being formed? We know that bone acts as a store of calcium to be drawn upon in time of need, just as subcutaneous tissue acts as a store of fat, and the liver as a store of glycogen. And, in answer to the question, "Is it possible that the calcium is needed and being diverted to other uses," we think of the growing fetus with its need for calcium salts as a factor always associated with the most common form of osteomalacia; namely, puerperal. And both chemical and clincal investigations show facts that are in accord with the hypothesis that the growing fetus takes up calcium salts at the expense of the maternal bones.[3]

Post-mortem examination of the pelvic bones of women dying during pregnancy shows mild signs of osteomalacia in so many that it seems to be almost physiological. And chemical observations of early osteomalacia during pregnancy show that the body is not losing calcium; it is even retaining calcium. In other words, there is, frequently, if not always, during pregnancy, a flux of calcium salts from the maternal skeleton to the growing fetus. But this is not followed by real osteomalacia except under certain conditions. The condition of greatest importance would seem to be a marked tendency to overprolongation of the period of calcium flux. Signs of osteomalacia rarely appear in early pregnancies. It is usually only after a series of rapidly succeeding pregnancies, with prolonged periods of lactation, that an attack occurs; and the patient usually recovers from the first one or two attacks. But retention of calcium and recovery do not begin at once at the end of pregnancy and lactation. There is a certain lag, and, furthermore, the lag is longer and longer in subsequent attacks until finally the condition becomes chronic. In other words, the flux of calcium, the increased bone catabolism, seems to be unduly prolonged after the original stimulus, for the flux is no longer present. Why this should be so, one can not say, but investigation shows that it is so. It would seem to be an example

of the overproduction which, as Weigert has pointed out, is characteristic of all tissue repair. It is analogous to the overproduction of free receptors which, according to Ehrlich's theory of immunity, is responsible for acquired immunity. Indeed, Harris, an English writer, who has recently given many examples of this "functional inertia," as he calls it, which leads to the continuation of processes for a time after the original stimulus has ceased, has pointed out that it is as fundamental a property of living matter as irritability itself.

The facts, then, in regard to the etiology of osteomalacia are that the beginning of the process is associated with a flux of calcium salts to the growing fetus, and that the flux continues after the need of calcium no longer exists. The tendency to prolongation of the flux, variable in different individuals, is very great in some, and in such susceptible persons, the increased catabolism of bony tissue lasts longer and longer after each pregnancy and begins earlier and earlier in subsequent pregnancies until finally the failure to make up for the losses leads to a bone very poor in lime salts and symptoms of osteomalacia appear.

The generally accepted belief that osteomalacia is a disease of the ovaries is based solely on the clinical facts regarding the supposed curative effect of castration. A clearer understanding of the etiology of puerperal osteomalacia makes the place of castration as a therapeutic measure clearer. Recovery from mild or early attacks of osteomalacia follows a variety of therapeutic measures and often even without treatment, but the advantage of castration over other measures lies in its prophylactic effect in making future attacks unlikely; and a careful examination of the clinical data shows facts that are in accord with this view.[4]

Osteomalacia occurs occasionally in persons other than pregnant women, and in these nonpuerperal cases the facts are in accord with the theory of osteomalacia already outlined, which associates the beginning of the flux of calcium salts with a need of calcium on the part of other tissue and which emphasizes the importance of the continuation of the flux after the need has been satisfied.[5] Cases have been reported where the calcification of a callus after a fracture was followed by osteomalacia, and in one of these cases the subsequent flux of calcium led to the excretion of 9 and 10 grams of CaO per day in the urine, 40 to 50 times the normal. I had the good fortune to be able to study carefully a case of nonpuerperal osteomalacia following the appearance of multiple osteomata, and the facts were in every way in harmony with the conception outlined. In 29 cases of metastic bone formation reported in the literature, in all but four some extensive destructive disease of bone was demonstrated.

To summarize briefly, then, our findings in bone metabolism: Bone, like other tissue, undergoes metabolism throughout life. Old bone is continuously being resorbed and new bone laid down. Under certain circumstances abnormalities may occur. In children, for example, where the new bone is normally increasingly richer in the calcium than the old, the abnormality may consist in the continued apposition of soft calcium-free bone which, bending under the increasing weight of the child, results in rickets. In adults a drain on the calcium store of the bones may be so great and long continued that the bone becomes soft and osteomalacia appears. The loss may be very localized, leading to osteitis deformans. In old age, when anabolic processes are less active, the building up of even lime-free bone may be so inadequate that osteoporosis may result.

As causes for the start of the drain on the calcium store may be noted pregnancy, growing bone tumors, fractures, metastatic bone formation, possibly arterio-sclerosis; and my attention has recently been called to a form of bowed legs seen in children about the time the epiphyses begin to calcify. Variations in the tendency to over-continuance of the calcium flux play an important part. These types of abnormal bone metabolism may be referred to as those leading to qualitative changes in the bone, and there are various subdivisions of this type.

Another kind of condition in which bone growth is involved is dwarfism.[6] The causes are probably many. But in one type I have observed a disturbance of calcium metabolism associated with improper development of bone. Calcium is almost absent from the urine, leading to the belief that the blood must be poor in calcium or contain it in some unusual combination. The feces are very rich in calcium, containing sometimes more than the food. There is, in fact, a flux of calcium through the feces. And in these cases the long bones fracture easily and X-ray examination shows a very thin cortex. In other types there are no abnormalities of this kind. Now, as pointed out by Rubner, we can imagine two fundamental causes for the lack of growth; one, the lack of what might be called the tendency to grow—that property which is present in young animals, but absent in adults—the other, the absence of the material for growth. And it seems to me that in these two types we have examples of disturbances of each of these two factors. In the one the skeleton is growing as fast as the material at its command permits. We might almost say that it is growing too fast, for it is growing in length at the expense of solidity. In the other there is no such tendency to grow. There is calcium enough present to form longer bones, but there is no tendency to form them. And this kind of disturbance of bone nutrition we may refer to as a quantitative change, for the bones fail to grow in size. There are two large subdivisions

of this type—one in which the tendency to grow is absent, the other in which the material for growth is not available.

[1] McCrudden, American Journal of Physiol., XVII, 1906. 32, and McCrudden, Jour. of Biol. Chem., 1910, VII, 199.

[2] Goldthwait, Painter, Osgood, and McCrudden, Amer. Jour. of Physiol., 1905, XV, 389.

[3] McCrudden, Archives of Inst. Med., 1910, V. 596.

[4] McCrudden Am. Jour. of Physiol., 1906, XVII, 211; McCrudden Jour. of biol. chem., 1910, VII, 185.

[5] McCrudden and Fales Arch. of Int. Med., 1912, IX, 273.

[6] See McCrudden and Fales J. of exp. Med. 1912, XV, 107; 1912, XV, 113; 1912, XV, 450; 1912, XV, 450; other papers in press at present. McCrudden J. of exp. Med. 1912, XV, 457; other papers in press.

THE RÔLE OF PROTEINS IN GROWTH.

Dr. LAFAYETTE B. MENDEL, Professor of Physiological Chemistry, Sheffield Scientific School of Yale University, New Haven, Conn.

The progress of physiology has brought an appreciation of two fundamental factors in growth, each of which has been the subject of misconception in the past. The primary feature in the secret of growth is the growth impulse, or what has variously been termed the "capacity to grow," "Wachstumstrieb," "Wachstumsfähigkeit" or "Wachstumsmöglichkeit." This is inherent in the organism itself and is peculiar to the species. The other modifying factor in growth deals with the nutrition of the individual. Each of these functions is amenable to experimental investigation.

In the past some confusion has existed regarding the interrelation of the food supply and growth. Obviously there is a minimum requirement of nutrient intake below which material gains are impossible in the growing organism. It must not be assumed, however, that growth, in its physiological aspects, is completely checked when the food consumption approaches the energy requirement for maintenance alone. The possibility of growth under adverse conditions of feeding has been discussed at length by Aron.[1]

Equally untenable is the view that abundance of food is the cause of growth in the formative period. Numerous observations have led to the conclusion that there is a direct proportionality between growth and the calorific value of the food intake; and upon this certain so-called laws of growth have been formulated. It must be borne in mind that such attempts at a mathematical expression of the facts of experience are based upon observations involving, with slight variation only, a single type of diet, namely, milk. Whether they will apply with equal force or accuracy when the range of our experimental experience with wider variations in the

qualitative make-up of the dietary has been somewhat extended remains to be seen. The older ideas regarding the heightened character of metabolism during growth have been modified by a better understanding of the conditions governing the energy exchange in general. The consensus of opinion at the present moment supports Rubner's contention that the metabolism in growth is essentially proportional to size, precisely as it is in adults.[2] The metabolism per unit of surface area is practically the same under comparable conditions of activity and diet.

Despite the importance of a comprehensive consideration of the calorific needs and the exchange of energy for the developing organism, it must not be allowed to overshadow or obscure the part which the individual nutrients play in growth. The chemical aspects of nutrition have a bearing quite as significant as the energy requirement. Only in recent years has science begun to furnish striking facts of the chemical and biological variations in the food and tissues of animals. Quoting from a recent address of my colleague, Dr. T. B. Osborne:

> It is evident that structural differences exist between very similar proteins of different origin, and it is interesting to note that chemically identical proteins apparently do not occur in animals or plants of different species unless these are biologically very closely related. In this respect the proteins are in marked contrast to the other constituents of plants and animals, for not only do identically the same sugars and fats occur in many species of plants and animals, but many of these are common to both forms of life. It thus appears that the chemical constitution of the proteins is closely connected with the biological relations of the forms of life which produce them, and that the morphological differences between species find their counterpart in the protein constituents of their tissues.[3]

The conflicting views which have been held since Liebig's time regarding the significance of protein in nutrition[4] have had their counterpart in the explanation of growth. Voit assumed that the protein metabolism of the growing organism is unlike that of the adult. "Es steht fest," he writes, "dass im noch wachsenden Organismus die Bedingungen für den Eiweisszerfall ungleich ungünstiger sind als beim Ausgewachsenen, womit eben das rasche Wachstum der Organen zusammenhängt."[5] In an important monograph on "Ernährungsvorgänge beim Wachstum des Kindes," Rubner[6] has duly emphasized the inadequacy of the theories which associated growth with a decreased power of protein katabolism in the body. He has, further, made it evident by his well-known researches, particularly with Heubner, that the diet of the infant is in general low in protein rather than the reverse, which is commonly assumed. How low the protein intake may remain is exemplified by the following data: For growth, 7 per cent of the total energy intake; for maintenance, 5 per cent of the total energy intake.

Quoting Rubner:

Gibt man aber grössere Eiweissmengen in der Kost des Säuglings, so folgt das Wachstum nicht der Eiweissmenge; das Wachstum ist eine Funktion der Zelle, es kann durch unzureichende Eiweisszufuhr latent werden, aber Eiweiss vermag nicht die Wachstumsschnelligkeit über die von der Natur gesteckten Grenzen zu heben (p. 110).

The well-known analyses of Bunge and Abderhalden,[7] showing the close parallelism between the rapidity of growth and the concentration of protein and ash in the milk of various species, have been cited as illustrations of a causal relation between proteins and growth. Of these interesting studies Minot has written:

It is obvious that the less the proteid in the milk, the longer does the species require to double its weight. This looks at first sight as if there were a relation between the composition of the milk and the period of growth of the animal; but you know very well that if you take the milk of a cow, which is very much richer in proteid material, and feed it to a baby, a human baby, that baby does not grow at the same rate as the young cow, but grows at the human rate. It is obvious, therefore, that it is somewhat more complicated than a mere question of food supply. We have here in fact one of the beautiful illustrations of the teleological mechanism of the body. These various species have their characteristic rates of growth, and by an exquisite adaptation, the composition of the mother's milk has become such that it supplies the young of the species each with the proper quantum of proteid material which is needed for the rate of growth that the young offspring is capable of. It is a beautiful adjustment, but there is not a causal relation between the proteid matter of the mother's milk and the rate of growth of the young. It is an example of correlation, not of causation.[8]

No one to-day will gainsay that marked chemical and biological differences exist between proteins from different sources. These inequalities have, until quite recently, not been made the subject of investigation in relation to their possible significance for nutrition. It has, as everyone knows, been intimated now and then that the supposed chemical unlikeness of the milk proteins of different species may influence their value in artificial infant nutrition. Some of the views have lost their justification by the later demonstration of the extent to which proteins are disintegrated prior to absorption and reconstruction, and of the synthetic power of organism.[9] The facts until lately available have, however, not justified any final pronouncement.

The question of relative digestibility has also ceased to evoke the widespread interest which it once attracted. How firmly erroneous doctrines may become established is exemplified in the long vogue which Biedert's teaching regarding the comparative indigestibility of cow's casein in the alimentary tract of the human infant has experienced. The incorrectness of this has been established by the demonstration that the assumed undigested casein flocks of the stools of infants nourished on cow's milk—upon the appearance of which Biedert's assumptions were based—are in reality not protein at all,

but as a rule are made up of insoluble soaps, etc. Indeed, Heubner and Czerny have both defended the adequate digestibility and harmlessness of the foreign milk proteins.

A strict comparison of proteins from unlike sources or of unlike properties was impossible so long as knowledge was lacking regarding the "building stones" which they can furnish. Now that it is clear that an individual constructs from its food proteins tissue proteins whose composition is decidedly unlike that of casein or its companion proteins in milk, too much stress need perhaps not be laid on minor differences in the content of different building stones. This does not imply that differences of composition are no longer of import in nutrition. The point to be emphasized is that the facts as yet at our disposal are too meager in most directions to enable this chapter to be closed. In certain fruitful fields of study, such as the interrelation of protein and inorganic salt metabolism, scarcely more than a beginning has been made. Furthermore, there has been a neglect of most of the dietary proteins aside from those of milk, despite the obvious fact that in both man and animals other foods enter largely into the dietary of the formative period.

Among the decisive reasons for the limited progress the lack of a really successful method of artificial feeding, i. e., the employment of mixtures of isolated foodstuffs has been foremost. That this plan of feeding approaches the ideal one was early recognized by Carl Voit. He wrote, in 1881:

> Zu dem Zwecke wäre es unstreitig am besten, könnte man nur reine chemische Verbindungen (die reinen Nahrstoffe) z. B. reines Eiweiss, Fett, Zucker, Stärkemehl, Aschebestandtheile, oder Gemische derselben geben. Da aber die Menschen und auch die Thiere nur selten solche geschmacklose Gemege auf die Dauer aufzunehmen oder zu ertragen vermögen, so bleibt für die meisten Fälle nichts anderes übrig als schon durch die Natur zusammengesetzte Mischungen (die Nahrungsmittel) zu wählen. Jedoch wäre es wohl möglich und ganz verdienstvoll, die Grundversuche, nachdem vorher der Weg mit Hilfe der letzteren Mischungen gefunden worden ist, mit den reinen Stoffen zu wiederholen, obwohl sich dabei sicherlich im Wesentlichen keine anderen Resultate ergeben werden.[10]

Röhmann[11] has conducted investigations for several years in this fashion, but the detailed results of his work are not yet available. Referring to experiments on mice he states (1908) that "die verschiedenen Eiweissstoffe eine verschiedene Bedeutung für die Ernährung und besonders für die Entwicklung jugendlicher Wesen besitzen."

Osborne and I have undertaken in the past three years to apply the method of feeding isolated food substances to the study of the rôle of proteins in nutrition.[12] The failures of earlier investigators are discussed in our Carnegie Publication 156, where the literature of the subject is reviewed. We early found that it is necessary to differentiate sharply between maintenance and growth in nutrition,

a distinction too frequently overlooked in the past. A man who maintains his weight may be in excellent nutritive condition, but a child which does likewise is failing to grow. One part of an organism may thrive at the expense of other tissues. The complexity of such relationships of proportionate growth demands consideration.

We have selected the changes in the body weight of the white rat as the most satisfactory index of the rate of growth in our experiments. This animal is easily reared and cared for, and its small size reduces the food requirement to a magnitude which falls within the range of experimental possibility where the preparation of special dietaries by laborious processes is a fundamental prerequisite. Furthermore, the longevity of this animal is, according to Donaldson, about three years; so that the first year of life corresponds to a long span in terms of human years. Not insignificant is the additional fact that the white rat has in recent years been made the subject of exceptionally extensive measurements in respect to growth and various features of development at the Wistar Institute in Philadelphia. In this way physical standards, so to speak, have been established for this animal. Monotony of diet and the possibility of maintaining rats in health for long periods under the enforced restraint of cage conditions have not proved to be hindrances to success. The records of rats fed for periods of one to two years on an unvaried daily diet leave no room for doubt in this direction.

It is scarcely necessary to remark that a suitable quota of inorganic nutrients must be furnished in every successful dietary. The importance of this gains an unsuspected prominence when one plans experiments with isolated food substances; for with the ordinary natural food mixtures a reasonable modicum is already provided. We are convinced from an extensive experience that many failures to promote growth in experiments on artificial nutrition have centered in the inorganic food ingredients of the selected dietaries. After very numerous failures to effect growth under artificial dietary conditions in which rats were still adequately maintained, it occurred to us to adopt the desired constituents from milk which has been found to contain the nutrient factors essential to success. By removal of fat and protein a "protein-free milk" was prepared containing the milk sugar in addition to inorganic salts and other as yet unknown components of the milk. This was at once found to facilitate growth remarkably when it supplied the inorganic components (and part of the carbohydrate) of the food. Thus by the use of "protein-free milk to furnish the "accessory" portions of the diet the relative deportment of different proteins in growth could be investigated. Latterly Osborne and I have further succeeded in imitating the inorganic make-up of the natural "protein-free milk" by uniting the various ions shown by analysis to be therein into an

artificial salt mixture.[13] This too has proved to be reasonably successful as a diet adjuvant; and the results furnish, so far as we are aware, the first published records of sucessful feeding experiments in which prolonged growth has been induced with carefully purified isolated foodstuffs and artificial salt mixtures.[14] By prolonged growth we refer to the capacity of the animals to triple or quadruple their weight.

From the outcome of the experiments directed especially to a consideration of the protein factor (which alone concerns us in this review) we can now report that growth can be induced by mixtures in which the nitrogenous component of the diet is furnished by a single, carefully purified protein. The simplest food mixtures with which characteristic growth curves have been obtained have been made up of only one protein, starch and sugar, and the artificial salt mixture, i. e., they have been fat—and, presumably, lipoid—free.[15] Adequate growth has been secured with casein from cow's milk, lactalbumin from cow's milk, ovalbumin from hen's egg, ovovitellin from hen's egg, edestin from hempseed, cannabin from hempseed, glutenin from wheat, glycinin from the soy bean, globulin from the squashseed, globulin from cottonseed, excelsin from the Brazil nut, and glutelin from maize.

Not all proteins suffice to promote growth under otherwise favorable conditions. The gliadin of wheat and rye (notably deficient in glycocoll and lysine, and rich in glutaminic acid) and the hordein of barley (closely resembling gliadin in chemical constitution) suffice for maintenance without growth. Animals nourished on them over long periods exhibit an interesting type of stunted condition resembling properly nourished younger animals which have attained the same body weight. The animals dwarfed by long periods of inappropriate protein feeding have not lost the capacity to grow. This easily attained form of animal infantilism offers opportunity for the investigation of numerous problems of broad pathological interest and scope.

The insufficiency of proteins for either maintenance or growth is exemplified in nutrition trials with the albuminoid gelatin and the alcohol-soluble zein of maize. On each of these the animals speedily decline. These proteins are not toxic per se; for with a suitable admixture of adequate proteins growth can apparently be restored. It is a significant fact that whereas satisfactory growth is possible with a wide variety of isolated single proteins as the source of nitrogen, adequate growth has not been observed with any of the various groups of proteins which are, from the chemist's standpoint, notably incomplete. It is far too early in our progress into the structural composition of the proteins to claim any even approximate conception of the chemical arrangement within these complex

substances; but we know that certain among those included in the list studied above lack one or more of the familiar amino-acids which are commonly constituents of the albuminous compounds. Thus wheat and rye gliadin as well as the hordein of barley, are deficient in glycocoll and lysine, while zein is further devoid of tryptophane.[16] Gelatin, with its lack of tyrosine, tryptophane, and cystine has long been known to be inefficient as the sole source of food nitrogen in animals. But it would be unjustifiable to postulate the nutritive inefficiency of a protein on the basis of the lack of a single amino-acid, at any rate; for casein, devoid of glycocoll, has proved to be most efficient as a source of nitrogen in animal growth.

Despite the fact that the modern methods of protein hydrolysis and amino-acid analysis indicate that these proteins are as "complete" as those of most other seeds, we have not, as yet, been successful in inducing growth with diets in which leguminous proteins, other than those from the soy bean, have been the sole sources of nitrogen in the diet. It is too early, however, to formulate any satisfactory explanation.

The methods of feeding introduced by us give a useful means of testing the protein requirement of growth under controllable conditions. From our observations on rats it has been noted that the lower limit of growth, under the conditions of diet represented and the protein used, was reached with about 6 per cent of protein calories in the food mixtures. With 14 to 15 per cent of protein calories an adequate growth rate was secured and this was not facilitated by an excess of protein over this amount.[17] Obviously, then, growth is not proportional to the protein intake although a certain minimum level of protein may lead to maintenance without growth.

Wherein the incapacity of some of the proteins used lies we are not prepared to say. It must be noted that growth has not been accomplished with any protein lacking the cyclic groups such as are found in tyrosine and tryptophane.[18] W. A. Osborne has indeed put forth the hypothesis that "cyclopoiesis" in this sense is a property of the plant cell, the animal organism being "acyclopoietic" and to this degree dependent on plant life for certain types of structural foods. That these "inefficient" proteins are not primarily toxic to the organism is shown by the fact that we have found many of them to be adequate for maintenance in both growing and adult organisms; whereas, as is well known, others like zein and gelatin by themselves do not even suffice for this function. Furthermore, admixtures of small proportions of efficient proteins suffice to induce growth or maintenance, as the case may be. It may not as yet be justifiable to claim a complete normal development of the individuals under the artificial conditions created. If we turn to

the familiar facts of infant nutrition, it has been pointed out that many children showing apparently adequate gains of weight may give evidence of anemic conditions and flabby musculature. When they are subjected to some unusual physiological strain they may collapse in ways not usual in the case of truly normal infants. In exemplification of this is the clinical picture occasionally presented by an "artificially" nourished infant. Further investigation, including both chemical and histological investigation of the tissues, breeding trials, immunity studies and other inquiries may be called for.

As I have written elsewhere, to the biological chemist no feature of these problems appeals more strongly, perhaps, than the question of how an organism can build such diverse nitrogenous tissues from a single dietary protein. It is true that the newer conceptions of the extensive rôle of hydrolysis in digestion prior to absorption have extended the inquiry a step further, so that we may ask what is the minimum of this or that amino-acid or simple polypeptide required. But we have seen rats grow for months with casein—thoroughly purified and presumably glycocoll-free—as the sole source of these amino-acids. During this time, one animal even brought forth two broods of young and secreted milk in sufficient quantity to bring her young to the age when they were able to care for themselves. Another pair of rats maintained 178 days on gliadin as the sole protein of the diet produced healthy young and successfully reared them. It is most unlikely, from all that is otherwise known, that the tissues of our experimental animals are chemically imperfect or essentially unlike those of normally fed rats which presumably do contain glycocoll and lysin groups. We are just beginning to appreciate the ultimate synthethic capacities of animal cells. Physiologists have been slow to admit the possibility of a synthesis of amino-acids *de novo* in the body. The evidence in the case of glycocoll seems beyond dispute.[19] Other accumulating data are beginning to point in the direction of the synthetic capacity of animal cells.[20] The construction of glycocoll in our growing rats, fed on the glycocoll-free protein casein, must be assumed, either in their body cells or possibly through the agency of symbiotic intestinal bacteria. And when it is recalled that all of our experimental diets are purine-free and some wholly free from organically combined phosphorus, the rôle of synthesis at once becomes more conspicuous. Phosphoproteins and nucleoproteins must be formed in such organisms through channels which unquestionably call for complex synthetic performances.[21] To what extent and in what directions these are possible remains for the future to disclose. The possibility of raising a young animal through the major part of its period of active growth, during which its body weight is multiplied several times, on a mixture of carefully

purified protein, starch, sugar, fats, and inorganic salts has been established. Thus some of the physiological problems with respect to the rôle of proteins in growth have been brought still nearer to the possibility of successful experimental attack.

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[1] Aron, H.: Wachstum und Ernährung. Biochemische Zeitschrift, 1910, XXX, 209; Nutrition and Growth, I. Philippine Journal of Science, B., 1911, VI, 1. See also Osborne and Mendel: Carnegie Institution of Washington, Publication 156, Part II, 1911, p. 67 fig. for some discussion of the literature on growth under adverse conditions of feeding.

[2] Cf. Schlossmann and Murschauer: Biochemische Zeitschrift, 1909, XVIII, 499; Howland: Zeitschrift für physiologische Chemie, 1911, LXXIV, 1.

[3] Osborne: The chemistry of the proteins. The Harvey Lectures, 1910–11, p. 72. J. B. Lippincott Co. Philadelphia.

[4] Cf. Mendel: Ergebnisse der Physiologie, 1911, XI, 460.

[5] Voit: Die Ernährung. Hermann's Handbuch der Physiologie, 1881, VI, 536.

[6] Rubner: Archiv für Hygiene, 1908, LXVI, 94.

[7] Cf. Abderhalden, E.: Zeitschrift für physiologische Chemie, 1899, XXII, 497; Bunge, G.: Physiologie des Menschen, 1901, LI, 122; as well as the textbooks of Abderhalden, Lambling, and others.

[8] Minot: The Problem of Age, Growth, and Death. New York, 1908, p. 108.

[9] Cf. Abderhalden: Synthese der Zellbausteine in Pflanze und Tier. Berlin, 1912.

[10] Voit: Hermann's Handbuch der Physiologie, 1881, VI (I), 19.

[11] Röhmann: Allgemeine Medizinische Central-Zeitung, 1903, No. 1; 1908, No. 9.; cf. Maly's Jahresbericht, 1903, XXXIII, 823; 1908, XXXVIII, 659 for the same abstracts; Biochemische Zeitschrift, 1912, XXXIX, 507.

[12] This work has been made possible by the cooperation of the Carnegie Institution of Washington. The results thus far reported by Osborne and Mendel are published in:

Feeding Experiments with Isolated Food Substances. Carnegie Institution of Washington, Publication No. 156, 1911, Part I, pp. 1–53; Part II, pp. 55–138.

The Rôle of Different Proteins in Nutrition and Growth. Science, N. S., XXXIV, 722–732.

The Rôle of Proteins in Growth. Proceedings American Society of Biological Chemists. Journal of Biological Chemistry, 1912, XI, No. 2, p. xxii.

Maintenance and Growth. Ibid., p. xxxvii.

Ein Stoffwechselkäfig und Fütterungsvorrichtungen für Ratten. Zeitschrift für biologische Technik, 1912, ii, 313.

Beobachtungen über Wachstum bei Fütterungsversuchen mit isolierten Nahrungssubstanzen. Zeitschrift für physiologische Chemie, 1912, lxxx, 307. Zeitschrift für physiologische Chemie, 1912.

Feeding Experiments with Fat-free Food Mixtures. Proceedings Society for Experimental Biology, April 17, 1912.

Growth and Maintenance on Purely Artificial Diets. Ibid., April 17, 1912.

Feeding Experiments with Fat-free Food Mixtures. Journal of Biological Chemistry, 1912, xii, 81.

The Rôle of Gliadin in Nutrition. Journal of Biological Chemistry, 1912, xii, 473.

Maintenance Experiment with Isolated Proteins. Journal of Biological Chemistry, 1912, xiii, 233.

[13] Cf. Osborne and Mendel: Proceedings of the Society for Experiental Biology, April 17, 1912; also Observations on Growth in Feeding Experiments

with Isolated Food Substances. Zeitschrift für physiologische Chemie, 1912, lxxx, 307.

[14] Compare, however, Röhmann: Biochemische Zeitschrift, 1912, XXXIX, 507.

[15] Osborne and Mendel: Feeding Experiments with Fat-free Food Mixtures. Journal of Biological Chemistry, 1912, xii, 81.

[16] For the properties of the vegetable proteins which have especially been selected for study, because of the readiness with which they can be subjected to adequate purification, see Osborne, T. B.: Ergebnisse der Physiologie, 1910, X, 47.

[17] In a review of the conditions leading to inanition in infants Rosenstern (Ergebnisse der inneren Medizin und Kinderheilkunde, 1911, VII, 390) says: "Eiweisshunger spielt im Säuglingsalter eine sehr geringe Rolle und kommt in Anbetracht des hohen Eiweissgehalts der Kuhmilch praktisch kaum in Betracht." The proportion of protein in the solids of human milk rarely exceeds 12 per cent.

[18] Cf. also Abderhalden, E.: Zeitschrift für physiologische Chemie, 1912, LXXVI, 22.

[19] Cf. Ringer: Journal of Biological Chemistry, 1911, X, 327; and Epstein and Bookman: Ibid., 353. The earlier literature is referred to in these recent papers.

[20] Cf. Knoop: Zeitschrift für physiologische Chemie, 1910, LXVII, 489; Zentralblatt für Physiologie, 1910, XXIV, 815; Embden and Schmitz: Biochemische Zeitschrift, 1910, XXIXX, 423; 1912, XXXVIII, 392; Kondo: Ibid., 407; Fellner; ibid., 414.

[21] Cf. McCollum, E. V.: American Journal of Physiology, 1909, XXV, 120; Abderhalden: Zeitschrift für physiologische Chemie, 1912, LXXXVI, 22; Fingerling: Biochemische Zeitschrift, 1912, XXXVIII, 448; McCollum and Halpin; Journal of Biological Chemistry, 1912, XI, xiii.

DIRECT CALORIMETRY OF INFANTS, WITH A COMPARISON OF THE RESULTS OBTAINED BY THIS AND OTHER METHODS.

JOHN HOWLAND, Professor of Pediatrics, Johns Hopkins University, Baltimore, Md.

By the determination of the respiratory exchange of infants a more intimate knowledge of their life processes has been sought. The earlier attempts in this direction were made with unsatisfactory apparatus, gave equivocal results, and lead to improper conclusions. It was not until 1898 and 1899 that trustworthy data were published by Rubner and Heubner. For many years this was the only information available. More recently the subject has received new interest by the publications of Schlossmann and Murschhauser and Niemann. By these authors the heat production of the infants, when determined, was calculated indirectly from the carbon dioxid excretion, with the aid of chemical analyses of the ingested food and the excreta.

In a series of experiments, the results of which I have published only in outline, the heat production was directly measured in addi-

tion to the usual determination of the carbon dioxide excretion and the oxygen consumption. This offers an opportunity for a comparison of the results obtained by the various experimenters. And yet comparison is difficult, for the reason that the observations have been made with different varieties of apparatus that have compelled the experiments to be carried on under widely differing conditions.

The experiments of Rubner and Heubner and Niemann were made with a modified Pettenkofer-Voit apparatus especially constructed for the purpose. But for reasonable accuracy with this apparatus determinations over long periods are necessary, and as the experiments were planned to ascertain the total daily metabolism they were carried out through as many hours of the 24 as possible, usually 20. The remaining 4 hours were passed out of the respiratory chamber while the infant was being fed and bathed. Even if we consider that this instrument is sufficiently accurate, and that the opening and closing of the chamber six times do not seriously interfere with the determinations, a great source of error is introduced by the child's being sometimes asleep and sometimes awake and active. The conditions of two experiments, even with the same child, are never comparable, for the effect of active exercise upon metabolism, even that of a small infant, is very great. It has been said that the amount of work that can be performed by an infant is insignificant in amount and not sufficiently large to cause much variation in the metabolism between waking and sleeping hours. Schlossman, however, found an increase of nearly 60 per cent in the carbon dioxide excretion of an actively crying child over the time when he was asleep, and, as may be seen from Chart I, I obtained differences in the heat production, directly measured, of 17.6 and 39 per cent between periods of quiet sleep and active struggling and crying.

A great difficulty with the use of the Pettenkofer-Voit apparatus lies in the fact that the metabolism of part, and part only, of the waking hours is determined. The four hours spent outside of the chamber are all waking and active periods, and the metabolism of these hours can not be measured or even approximately estimated, for it would not be fair to consider the respiratory exchange during this period equal to that of a similar period spent within the chamber, and the periods of waking and sleeping of a child in a metabolism frame that can not be reached to be quieted are not as regular as those of one not in such a position. It is probably on this account that results from day to day with the Pettenkofer-Voit apparatus, even with the same child, have varied so greatly. Thus, in one experiment lasting six days and divided into three periods of two days each, the heat production in the first period was 1,200 calories per square meter of body surface; in the second period, 1,355 calories; and in the third period, 1,436

calories. The carbon dioxide excretion rose from 180.2 grams per day to 217.9 grams in the same experiment. It is likely that with an average of a great many days, and with a child accustomed to the experiment, the error due to this cause would be reduced, but it seems probable that the lowest figure obtained, rather than an average of many figures, would give a result more nearly like that that would be found provided normal conditions could obtain. The criticism of this method must therefore always remain that, while it gives the carbon dioxide excretion and, by calculation, the heat production of the greater part of a day, which neither of the other forms of apparatus can do, the results, when applied to a whole day, as is usually done, can be at best only approximate.

The Zuntz and Oppenheimer modification of the Regnault-Reiset apparatus, with which Schlossmann's observations were made, compels different conditions of experimentation. The determinations can never be interrupted as resumption is impossible. The periods must therefore be of short duration to allow for feeding. Calculations of the heat production with the aid of this instrument have rarely been attempted, but it directly determines the carbon dioxide and oxygen. Schlossmann and his coworkers had difficulty in obtaining long periods of sleep, even at night, and they early recognized that the unavoidable movements during the waking hours had a marked influence upon the carbon dioxide excretion. They believed, also, that the effect of starvation was shown during the last four hours of an eight-hour period. For these reasons, in all of their recent experiments, only short periods have been used.

The theory of the Atwater-Rosa-Benedict apparatus, with which I have worked, does not require detailed description. It directly measures the heat production, as well as the carbon-dioxide excretion and the oxygen consumption. It early became apparent to us, just as it did to Schlossmann, that muscular exercise had such a profound effect on the carbon-dioxide excretion and the heat production, as may be seen from the protocols of many of the experiments, but particularly from the two to which I have drawn attention, that comparable conditions could not obtain except during quiet sleep. For this reason, although the metabolism of many waking hours was determined, only that of the sleeping hours has been used for comparison.

In order to induce as quiet sleep as possible, the infants were accustomed to wearing the rectal thermometer for several days before the experiments, and were kept awake during the forenoon. In the afternoon, after being fed and put into the calorimeter, they almost always went promptly to sleep. It was possible to tell by observation and by the variations of the temperature of the air in the calorimeter and of the child's temperature whether he was

quiet or not, but the ingenious method of Benedict will, in future experiments, allow of still better control in regard to this. With this apparatus, just as with the Zuntz-Oppenheimer apparatus, we are enabled to compare the energy exchange of infants and the effect on this of the different foods and of different environment. But we can not determine the metabolism of a whole day.

As concerns the accuracy of the various forms of apparatus, it seems only fair to demand that all control determinations of carbon dioxide and oxygen be made with amounts as small as those that would be determined in the case of an infant. This has usually not been the case. But the calorimeter with which my results were obtained leaves little to be desired in point of accuracy. It was designed and constructed by Dr. H. B. Williams especially for infants and small animals. Numerous control experiments showed that the error in carbon dioxide and oxygen with amounts of 5 to 7 grams per hour was not more than 2 per cent, and that the error in the heat determination of 10 calories per hour was 2½ per cent or less.

Greater accuracy than this is not required and appears unimportant to strive for when the very great error which occurs in any method of determining the surface area of an infant is considered. This is an important factor in preventing an accurate comparison between the results obtained with different infants, and yet it is in terms of surface area that we must compare them since the enunciation of the law of Rubner.

The determination of the surface of human beings was first undertaken by Meeh. His object was to obtain a formula for all ages and his observations included only three infants, and these well nourished. The basis for his formula was the determination of Moleschott that the volume of bodies of similar composition varies in the ratio of the cube root of their weight, and that their surface areas vary in the ratio of the square root of their volume. The difference between the figures obtained in this way and those from actual measurement allowed Meeh to determine a constant by which his figures could be multiplied and reasonably accurate results obtained. But he appreciated that for children a different constant should be used than for adults, and that a smaller one. For this reason Rubner and Heubner employed as a constant 11.9 instead of Meeh's 12.8.

More recently, Lissauer has pointed out that for any but the well nourished, and sometimes for these, the constant is very much too large and, on the basis of 12 measurements of his own, almost all upon poorly nourished children, he has proposed 10.3 as a constant. Now while it is true that the formula with the constant 11.9, which Rubner and Heubner and Schlossmann have used, is quite accurate for exceedingly well-nourished children, but not always, as one error of 15.5 per cent shows, it is very inaccurate for poorly nourished

children, and yet by these authors it has been used for all the infants with which they have experimented, well nourished and poorly nourished alike. It is apparent that a formula is required that is more accurate and at the same time applicable to both the well and the poorly nourished. Simplicity of calculation is also to be desired. In the endeavor to supply such a formula, Mr. R. T. Dana and the writer made use of the data furnished by Meeh and Lissauer and expressed them in a formula of the $y=mx+b$ form, by means of which the desired simplicity and greater accuracy and applicability are obtained. There is no reason to question the reliability of the measurements of Meeh and Lissauer, and we have, therefore, employed all their measurements but one, which was so decidedly abnormal and, with any formula, gave such a great error that it should not be considered in the construction of a formula that is intended to express the results obtained in a general form.

We first determined that the length of the child, the circumference of the chest, abdomen or head bore no constant relationship to the surface area and need not, therefore, be included in a formula, but it was, of course, readily seen that the weight bore a very constant and important relationship. The data were plotted, as Chart II shows, and a curve drawn which appeared to represent in the best way the conditions. This curve, by its distances from the axes ox and oy, represents an average of the observed conditions so that, when drawn to the proper scale, the point on the curve or line corresponding to any known weight of child may be marked on the chart, and the corresponding area read off directly. Thus, if we have an infant weighing 7,000 grams and we desire to know his surface area, we find where the 7,000-gram line intersects the curve. From this point, carrying a line horizontally to the left, we find that it intersects the y axis at a point corresponding to 4,100 square centimeters. The small circles on the chart are indicative of the 14 observations given in the table. The curve was drawn as nearly as possible to all these points, so that the average distance from any point would be as small as possible.

In the formula $y=mx+b$, which is the algebraic representative of this geometric figure, x and y represent the abscissas and ordinates of the curve, b represents the distance along the y axis from the origin to where the curve intersects the y axis and m represents the tangent of the angle that the curve makes with the x axis.

In this formula, y represents the surface area of the child, x represents the weight of the child in grams, m represents 0.483 and b represents 730 square centimeters. Having these last three quantities, it becomes possible to obtain the y or surface area by simple computation. The amount for b was read directly from the chart and m was obtained by dividing 5560—730 by 10000. This

formula has the advantages, as compared with those of Lissauer and Meeh, that it is more accurate and more generally applicable; it is much simpler and is elastic. The relative accuracy of the various formulas is shown in a comparative table (Chart III), giving the calculated surface areas compared with the measured areas. It will be observed that the gross error for the 14 cases compares as follows:

Meeh's original (12.3 constant)	12.4	per cent too large.
11.9 constant	9	per cent too large.
10.3 constant	5	per cent too small.
$y=mx+b$	0	

whereas the individual errors show less departure from, and greater consistency with, the observed facts, by means of the new formula, than by any of the others.

The table also shows that the formula gives satisfactory results for all classes of children, the well and the poorly nourished, while the other formulas that have been proposed are not accurate in this respect. Thus, Meeh's formula, with the constant 12.3 or 11.9, is fairly satisfactory for well-nourished children, but very bad for the poorly nourished, while almost the exact opposite may be said of the formula with the constant 10.3. The formula $y=mx+b$, compared with the others, is very simple and requires only a simple multiplication and one addition. A still simpler method of computing is by direct readings from a readily constructed chart, such as the one shown. This formula has been constructed from the data at present available, and can readily be applied to any future observations that may be made. No elaborate calculation is necessary for this purpose. Future data may be plotted upon a chart, and, if it seems desirable to establish another curve which would better fit the then existing facts, the same can be done at sight, and the new constants computed at a moment's notice.

On account of the advantages of this formula, I have calculated my results with it, and, for comparison, recalculated the results of others.

In my experiments, short periods only were used. Therefore, in order to keep the metabolism as regular as possible, the infants were fed at 4-hour intervals throughout the 24 hours, or six times daily. They were put into the calorimeter immediately after a meal at 1 p. m. and the experiment begun shortly before 2 p. m. It was generally continued for 3 hours up to the next feeding time.

The first child whose metabolism was determined was a healthy boy of 3 months. He weighed 4.77 kilograms. His food was a mixture of milk and water, equal parts, with 5 per cent milk sugar added. Of this mixture he was given 200 cubic centimeters every 4 hours, a food value of 115 calories per kilo. In the food he received 2.98 grams of nitrogen and eliminated on 2 days, when his urine was collected, 1.61 grams of nitrogen and 1.76 grams nitrogen. His nitrogen retention was, therefore, good. He had been gaining weight

slowly but steadily, and his digestion was normal. On the chart, for simplicity's sake, I have kept the weight the same throughout the first series of experiments, though he gained in these two weeks 230 grams. In February, he suffered from an attack of influenza that reduced his weight markedly. When he had recovered and was again in a normal condition and gaining weight slowly, he was again used in the experiments.

His metabolism in the two periods differed by less than 3 per cent. On the ordinary simple diet, the average heat production directly measured during 11 sleeping hours was 13.76 calories per hour, or 1,094 calories per square meter of body surface per day.

The average carbon dioxide excretion on the ordinary diet and during the sleeping hours was 17.01 grams per square meter of body surface per hour.

A comparison of results of others, so far as the heat production is concerned, with those that I have obtained is nearly impossible, as the heat production has not before been directly measured. Carpenter and Murlin determined the heat production of sleeping newly born infants by the difference of the heat production directly measured of the mother with and without her child. The average heat production of these infants was calculated to be 895 calories per square meter per day. This, however, is a rough method of determination, and Carpenter and Murlin especially emphasized the fact that the warming of the child by the mother may have influenced their results.

The determinations from which Rubner and Heubner and Niemann were able to calculate the energy exchange in their experiments were made without reference to waking or sleeping, and, therefore, as might be expected, in all but one instance their results were considerably higher than those obtained with my child at rest. Rubner's and Heubner's first child was 5 weeks old and nursed at the breast. The heat production of this child was 1,118 calories per square meter per day. Their second child, 7½ months old and fed on cow's milk, had a heat production of 1,348 calories. The third child, an atrophic infant of 3½ months, when fed on cow's milk produced heat equal to 1,284 calories, and when given a proprietary food produced heat equal to 1,223 calories per square meter per day. It would appear that there were two reasons that accounted for the low heat production of the breast-fed child: First, and probably most important, that he was very young and hence sleeping and quiet most of the time; and, second, that he was given an insufficient quantity of food (as he lost weight in the experiment) with a low protein content. Niemann's experiments were all made with the same child between the ages of 4 and 9½ months. On a variety of diets he had a very regular heat production in the different periods of 1,486, 1,408, 1,442, and 1,492 calories per square meter per day.

As the difference in the method of performing the experiments accounts for an increased heat production, so, also, it accounts for a greater excretion of carbon dioxide. All the experiments of Rubner and Heubner and Niemann showed a higher figure for carbon dioxide, except those in which the infants were given a proprietary food insufficient for their nutrition, and that in which the very young infant was given breast milk.

Schlossmann's experiments determined only the respiratory exchange. In those in which the infants were fed the carbon dioxide excretion was considerably lower than I obtained, although the conditions of the experiments were the same. In one, however, the 17.17 grams per square meter per hour were almost exactly like my figures.

One experiment with this first child was made to show the effect of 18 hours' deprivation of food, the child receiving only weak tea sweetened with saccharine. It has been a subject of contention whether after 18 hours the fasting metabolism was reached. Schlossmann found a diminished carbon-dioxide excretion during such periods, an average for his children of 13.7 grams instead of the 15.1 grams per square meter per hour, which he obtained with children that were fed. Rubner and Heubner and Niemann found a decided diminution in the output of carbon dioxide when an insufficient proprietary food was given to two children. While Rubner and Heubner calculated a heat production somewhat below that when cow's milk was given, Niemann found no lessening in the total heat production. With my fasting child there was no diminution in the total heat production, it being 1,106 calories per square meter, calculated for 24 hours.[1] The carbon dioxide excreted was lessened when an average of the first two hours of that period is taken, even though during part of the second hour the child was awake. It was 16.23 instead of 17.01. The respiratory quotient for two hours was 0.81. This experiment, in so far as one can do so, brings additional proof to the view that insufficient food reduces the carbon-dioxide excretion, but that, after 18 hours, a fasting metabolism is not reached with infants, as shown by the normal heat production and by the respiratory quotient of 0.81.

The second child was a small but very vigorous and active boy of 7 months. He weighed 4.32 kilograms, and had gained well during the month before the experiments. His digestion was good, and he was essentially normal, except for his small size. His food was three-fifths milk with 5 per cent milk sugar added and 30 grams of malt extract and had a food value of 132 calories per kilogram. He took

[1] It is probable that during this hour there was some activity that was not noticed. There would certainly be a somewhat lower metabolism when no food was ingested than after a full meal.

3.58 grams of nitrogen in this food and excreted 2.20 grams in the urine. The average of the heat, measured on different days during seven quiet sleeping hours, was 14.91 calories, or 1,270 calories per square meter of body surface a day, considerably higher than the 1,094 of the first child. The carbon-dioxide excretion was 5.41 grams per hour, or 19.21 grams per square meter per hour.

I was formerly of the opinion that the higher metabolism of this child was more apparent than real, and was due to an error in the surface area, calculated by a formula which failed to include the variable of length. Since it is apparent, from a study of the measurements of Meeh and Lissauer, that the length bears no constant relation to the surface area, the explanation must be sought in the greater quantity of food that the second child received, 132 calories per kilo, as compared with 115 calories per kilo. The protein was somewhat in excess in the food of the second child, and 30 grams of malt extract were also added to it. The effect of an excess of protein has been greatly emphasized, but not so much influence has been ascribed to an excess of sugar. Lusk has, however, recently shown that a large quantity of this may increase markedly the metabolism, and it appears that in this case it produced a decided effect when added to a diet already generously sufficient to supply the child's caloric requirements.

With both of these children experiments were made to determine if an excess of nitrogenous food would increase the heat production. Rubner and Heubner have explained the higher metabolism of their bottle-fed child over the breast-fed child by the specific dynamic effect of the greater protein content of the cow's milk.

With the first child 15 grams a day of nutrose were added to his ordinary food, 5 grams to each of the first three feedings for several days. Nutrose contains 14.25 per cent nitrogen. This increased the nitrogen of the food from 2.98 grams to 5.12 grams and that of the urine from 1.76 to 2.72 grams. The effect was marked on two days on which determinations were made, and the result was an average increase from 1,094 to 1,210 calories per square meter per day, or a little over 10 per cent. While on his usual diet 14 per cent of his heat production was from protein food. On the high protein diet 20 per cent was from protein food.

To the ordinary food of the second child 30 grams of nutrose were added for three days, and on the last two of these his metabolism was determined. The results obtained during five hours of these days are available for averages. The effect was very striking. The heat production rose from 1,270 to 1,595 calories per square meter per day, an increase of 26 per cent above that with the ordinary diet. With the addition of nutrose his food contained 7.85 grams of nitrogen, and he excreted 4.46 grams in his urine, more than twice as much as before.

On his ordinary diet 16 per cent of his heat production was from protein, and when the nutrose was added 26 per cent of the heat production was from protein. The view that the specific dynamic effect of the protein is due alone to the rapid metabolism of protein does not appear substantiated by these experiments. In each instance, but particularly in the case of the second child, the increased protein metabolized, as shown by the nitrogen of the urine, fails to account for all of the increased heat production or for the extra carbon dioxide of the respiration. With the second child there was 50 per cent more heat actually measured than could be accounted for by the metabolism of protein alone and 0.37 gram more carbon dioxide. This calculation, therefore, affords evidence for believing that the protein (or more probably its decomposition products) acts also as a stimulus to the metabolism of all the foodstuffs.

In addition to the experiments on comparatively normal infants, two were made with very poorly nourished and emaciated children. The first was a boy 6 months of age, who weighed 3.05 kilos. He had been in the hospital several times and had been discharged each time while gaining weight, but was always brought back in a condition of extreme malnutrition, having received the worst possible care at home. He was literally skin and bones, with no fat, and very little musculature. Before the experiment, he had gained a few grams, and his digestion was fairly good. He was given two-fifths milk with 5 per cent milk sugar added, and took 150 cubic centimeters every four hours, a food equivalent to 117 calories per kilogram. Satisfactory determinations were made on two different days. His heat production was low, 7.94 calories per hour or 865 per square meter per day. The carbon dioxide excretion was also low—15.14 grams per square meter per hour.

Still more striking were the results obtained with an 8-year-old child, emaciated to a most extreme degree and almost devoid of musculature. She had suffered from cerebro-spinal meningitis six and a half years before, and was left idiotic with contracted extremities. She weighed only 5.9 kilograms when admitted to the hospital, but had gained very rapidly, and the experiments were made when her weight was 6.6 kilograms. Her digestion was always good. She took 200 cubic centimeters of milk every four hours, or 100 calories per kilogram per day. Three of the experiments were entirely satisfactory; she slept all of the time while in the calorimeter. The average heat production was 13.23 calories per hour or 809 per square meter per day.

The average carbon dioxide per square meter per hour was 12.3 grams. If the surface area of this child were calculated according to Meeh's formula with a constant of 12.3, the heat and carbon dioxide production would appear to be very much less. Rubner's and Heub-

ner's marantic child, evidently in not nearly so emaciated a stage as either of these, had practically no diminution of heat production or carbon dioxide excretion on a cow's milk diet. Schlossmann's marantic children showed a slight decrease in their carbon dioxide excretion as compared with his normal children, but the infants were not nearly so malnourished nor was their relative decrease in carbon dioxide nearly so marked as I have found. The low heat production of both of these children who were generously fed can, if the calculation of the surface area be correct, be explained only by the great deficiency of vital functionating muscular tissue. The furnaces for the production of heat are lacking. While the law that the heat production is proportional to the surface area of the body applies for the well and even moderately nourished, it does not seem to apply for the greatly emaciated child, with almost complete absence of muscular tissue. But it must not be overlooked that the formula may give a surface area much too large for such greatly emaciated children. Further observations and further measurements should be made.

Finally, I should like to speak of the close comparison, in my experiments, between the heat production directly measured and that calculated by the method of Zuntz and Schumberg. On four days with the first child, and two with the third, the urine was collected for 24 hours and, from the nitrogen excretion and the oxygen consumption, an indirect determination of the heat production calculated, on the assumption that the nitrogen excretion throughout each period was uniform. This assumption appeared justified by the frequency and uniformity of the feedings. It is seen that the agreement is very close, not only in the total observations for the children, when in each instance the difference was less than 1 per cent, but for each day when the difference was not more than 3 per cent, and the 3 per cent difference was on a day when only one hour was available for the determination. When two or more hours were used the difference was 2 per cent or less. This not only acts as an excellent control on the heat production, as actually measured, but shows plainly that it is possible, in the majority of instances, to calculate the heat production with an entirely reasonable margin of error, when the respiratory exchange and the nitrogen excretion are known. Calorimeters for the direct measurement of the heat production are very expensive to build and operate, and require a large force of trained workers. When an apparatus is devised which will measure the respiratory exchange within limits narrow enough so that it may be accurately applicable to children it will be possible for many workers to make the observations that are now allowed to only a few, and so greatly to add to our knowledge regarding the metabolism of infancy.

CHART I.—*Effect of exercise.*

	Calories per hour.	Calories per square meter per day.	Increase.	Behavior.
			Per cent.	
Child 1	13.72	1,186	.....	First hour sleeping.
	15.21	1,226	.....	Second hour awake.
	16.13	1,381	17.6	Third hour crying.
Child 2	14.85	1,265	.....	First hour sleeping.
	17.15	1,484	.....	Second hour awake.
	20.58	1,753	39.0	Third hour crying.

CHART II.—*Curve of surface area.*

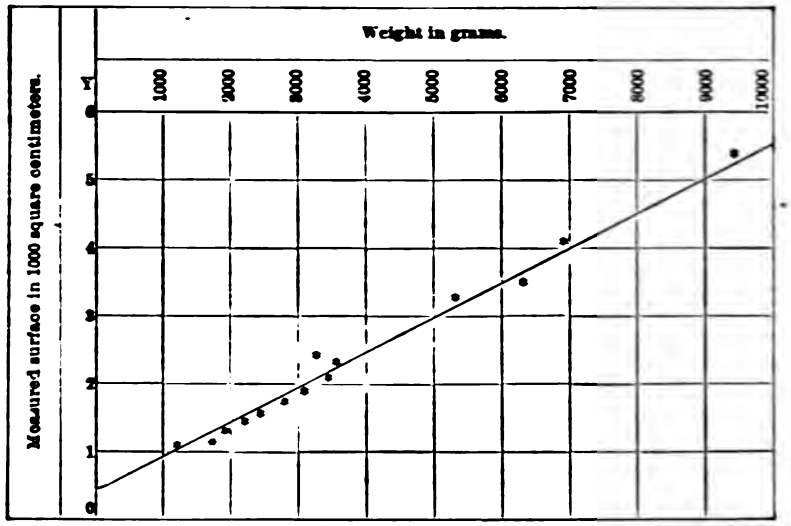

CHART III.

No.	Surface (square centimeters).	Weight.	$12.3^{\frac{2}{3}}/Wt.^{\frac{2}{3}}$	Per cent of error.		$11.9^{\frac{2}{3}}/Wt.^{\frac{2}{3}}$	Per cent of error.		$10.3^{\frac{2}{3}}/Wt.^{\frac{2}{3}}$	Per cent of error.		$y=mx+b$.	Per cent of error.	
				+	−		+	−		+	−		+	−
1	1,462	1,380	1,450	.....	0.8	1,403	.....	4.0	1,215	.....	16.9	1,348	.....	7.78
2	1,482	1,730	1,773	19.2	.....	1,715	15.7	.....	1,485	0	.....	1,566	5.66	.....
3	1,610	1,960	1,926	19.6	.....	1,864	15.8	.....	1,613	0	.....	1,677	4.16	.....
4	1,766	2,320	2,081	17.7	.....	2,013	13.8	.....	1,742	.....	1.5	1,803	1.98	.....
5	1,866	2,500	2,286	21.4	.....	2,192	17.4	.....	1,897	1.7	.....	1,940	3.97	.....
6	2,002	2,900	2,501	19.6	.....	2,420	15.7	.....	2,095	0	.....	2,132	1.91	.....
7	2,116	3,400	2,615	23.6	.....	2,530	19.6	.....	2,190	3.5	.....	2,229	5.34	.....
8	2,230	3,370	2,764	24.0	.....	2,675	20.0	.....	2,315	3.8	.....	2,360	5.82	.....
9	2,420	3,270	2,710	12.0	.....	2,622	8.3	.....	2,269	.....	6.2	2,311	.....	4.51
10	2,505	3,920	2,575	2.8	.....	2,490	.....	.6	2,150	14.1	.....	2,190	.....	12.55
11	3,292	5,220	3,706	12.6	.....	3,586	8.9	.....	3,103	.....	5.7	3,260	.....	.97
12	3,470	6,180	4,142	19.3	.....	4,007	15.5	.....	3,469	0	.....	3,715	7.07	.....
13	4,222	6,766	4,310	2.1	.....	4,260	.9	.....	3,685	.....	12.7	4,005	.....	5.15
14	5,345	9,514	5,530	3.5	.....	5,350	0	.....	4,630	13.4	.....	5,330	.....	.28
Total.	35,880	.....	40,349	12.4	.....	39,127	9.0	.....	33,858	.....	5.7	35,866	.....	0

CHART IV.—*Average heat production and CO_2 excretion.*

	Age.	Weight (in kilograms).	Calories per square meter per day.	CO^2 per square meter per hour.	Food.
Child 1	3 months	4.77, 4.65	1,094	17.01	Cow's milk.
Do	do	do	1,106	16.23	Fasting.
Child 2	7 months	4.32	1,270	19.21	Cow's milk.
Child 3	6 months	3.05	865	15.14	Do.
Child 4	8 years	6.60	809	12.3	Do.

CHART V.

Author.	Food.	Age.	Weight.	CO_2		Heat production (calories per square meter per day).
				Per hour.	Per square meter per hour.	
			Kilograms.			
Rubner and Heubner	Breast	5 weeks	5.0	4.72	15.01	1,118
Do	Cow's milk	7½ months	7.64	7.92	18	1,349
Do	do	3½ months	2.96	4.23	19.47	1,284
Do	Kindermehl	do	2.96	3.6	16.69	1,225
Niemann	Buttermilk and sugar	4 months	5.12	6.9	21.55	1,486
Do	Skimmed milk and sugar	5½ months	5.9	7.7	21.55	1,498
Do	Kufeke Mehl	9 months	5.57	5.9	17.26	1,462
Do	Cow's milk	9½ months	5.98	6.9	19.08	1,497
Schlossmann	Breast	4½ months	5.79	5.29	14.99	.....
Do	do	9½ months	8.45	6.95	14.44	.....
Do	do	12½ months	8.93	6.95	13.77	.....
Do	do	.....	6.31	6.49	17.17	.....
Do	Fasting	6 months	5.01	.....	13.97	.....
Do	do	do	5.11	.....	13.57	.....
Do	do	5 months	4.22	.....	13.94	968
Do	do	do	4.43	.....	14.22	
Do	do	3 months	4.98	.....	13.73	.....
Do	do	do	5.04	.....	12.77	.....

CHART VI.—*Effect of excess of protein.*

	Food.	CO_2 (per square meter per hour).	Calories (per square meter per day).	Increase.
				Per cent.
Child 1	Ordinary	17.01	1,094	.....
Do	Nutrose added	18.21	1,210	10+
Child 2	Ordinary	19.21	1,270	.....
Do	Nutrose added	23.64	1,595	26

CHART VII.—*Heat production (directly and indirectly measured).*

	Food.	Calories per square meter per day.		Difference.
		Measured.	Calculated.	
Child 1.	Ordinary	1,046	1,084	2 per cent.
		1,113	1,174	
		1,196	1,164	
Do.	Nutrose added	1,218	1,179	3 per cent.
Do.	do	1,204	1,180	Less than 1 per cent.
		1,235	1,212	
		1,181	1,250	
		1,106	1,177	
Do.	Fasting	1,226	1,156	Do.
		1,301	1,243	
Child 3.	Ordinary	858	793	2 per cent.
		913	933	
Do.	do	825	840	Do.

INFLUENCE OF QUALITY AND QUANTITY OF THE FOOD UPON THE GROWING ORGANISM.

Dr. HANS ARON, Chief of the Scientific Laboratory of the University Children's Clinic, Breslau, Germany.

While the growth of the plants under manifold conditions of nutrition as produced by soil and fertilizers has been carefully investigated in various directions, we have but a limited knowledge of the influence of the quality and quantity of the food on the growing organism of higher animals and human beings. As a small number only of the manifold problems offered by this theme has been investigated experimentally, many important and interesting questions can not yet be answered at all. And following the invitation of Dr. Chittenden, as president of this section, to describe the influence of the food upon the development of the growing animal organism, I can not give here a well-finished picture, but only a review of those facts which appear somewhat proven by experiments.

The rhythm of cell division, called "Wachstumpotential," by Escherich, is limited for every class of animals and for every individual; therefore, even with the greatest intake of food growth will never exceed a certain limit. The conditions of nutrition can never accelerate the process of growth, but only can restrain the development of the juvenile organism, either because the quantity of foodstuffs taken is not sufficient to warrant a normal process of growth or because the food is lacking one or more of the building stuffs which are needed to build the growing body.

A very important chapter of this theme, the influence of the proteins on the process of growth, has been treated already by Lafayette

B. Mendel, and I beg to be allowed to refer to his review. The protein-free organic foodstuffs, while principally used for furnishing energy as combustible materials, at the same time present the building material of which are formed the protein-free organic constituents of the growing body. For this reason, an insufficient quantity of a food otherwise suitable and of normal composition being given, the process of growth necessarily can not proceed in its normal way.

Experiments made by Waters on calves, by myself on dogs, and recently on rats, have shown, in accordance with clinical observations by Camerer, Freund, and Variot, that a growing organism, when limited in its intake of food even so severely that the energy required for maintenance is not covered, will draw upon its reserve materials, principally fat, and at least in the beginning the process of growth will not stop entirely. Of course, only certain parts of the body will grow, i. e., increase in mass and go on to develop. This is true of bones and brain, while others, like fat and sometimes muscles, will decrease in weight. In this way the normal proportions of the body are lost, and it is quite right to call the process now going on a disproportionate growth, the principal characteristic of which is a relative increase of the skeleton. This progress of the growth in the bones during a period of insufficient nutrition when the weight comes to a standstill or even decreases slightly can already be noticed by the appearance of the animals; it is better seen from measurements of the body length and most clearly by X-ray pictures. Analyses of animals kept on constant weight by an insufficient intake of food, compared with those of normal animals of the same weight but of correspondingly younger age, will show that during such a period of constant weight the fat has decreased considerably, being partly replaced by water, and the mineralic constituents have increased twice or even more; further, that the quantity of protein of the muscles became smaller and that of the bones larger.

After a certain period of insufficient food intake, the reserve materials have nearly disappeared, and by and by the bones will cease to grow any further. If the animal now is given at least such a quantity of food as will furnish the materials needed to maintain its body, it will keep alive and stay as it is, of course remaining behind its normal brothers considerably in weight and size.

It is a question of great theoretical interest and practical importance whether those animals, stunted by insufficient supply of a normal diet, later, when fed amply, can grow and develop like normal animals; or whether their capability to grow has materially suffered by checking the growth during a certain period. Animal experiments and observations of babies show clearly that the young organism will overcome short periods of restrained growth of a few

days or, with slower growing animals, even of weeks, without trouble. If the period of restricted food was of longer duration, and a well pronounced disproportionate growth and, later, a standstill of growth, had already taken place, the capability to grow is not diminished. In recent experiments, which have not yet been published elsewhere, rats were kept at a constant weight until their normal brothers reached a weight three to four times of that of the stunted animals. When now fed amply, these stunted rats were still able to grow at normal rate and reached the weight and size of a normal rat, only delayed for about a time corresponding to the period in which the growth had been checked. However, when the restriction of diet and the standstill of the processes of growth extend over the entire period of "youth," the capability to grow may apparently disappear.

I had two dogs about 3 months of age, the one of which was fed normally, the other was kept at a constant weight for 310 days, then was fed amply for 150 days. During this second period the dog increased in body weight and the animal, formerly emaciated, became fat and showed well-rounded form, but did not increase materially in length. Thus, at the five-hundredth day of experiment, we saw an animal considerably smaller than the normal brother, but thicker and fatter.

I am inclined to believe, from a few experiments made so far, that the age at which we stunt an animal by restriction of diet is of great importance, and it seems to me very probable that the restriction of diet it the more deleterious the younger the animal is, especially during the period of lactation.

The question whether fats and carbohydrates will replace one another as well, as building materials for the growing organism, as they do in furnishing energy, is very hard to answer, on account of the fact that food free of carbohydrates and rich in fats mostly will cause severe indigestion. On the other hand, Mendel and Osborne quite recently have shown that young rats fed with an artificial mixture of foodstuffs free of fat developed like normally fed animals. These same experiments also may be taken as a proof that the growing animal organism does not demand any other organic building materials besides proteins and carbohydrates.

It has been mentioned that by overfeeding the processes of growth can never be promoted above a certain limit, but Mast can be produced in growing animals like in adults by an ample supply of organic foodstuffs. Fattening, while mainly caused by a certain individual disposition, is only possible when the intake of organic foodstuffs is increased; and the fat content of an animal is, in the first place, an expression of the nutritive conditions. If we disregard the content

of fat, which varies considerably with different individuals, the rest of the body mostly shows quite a constant composition in animals of like race and age. According to Steinitz and Weigert, upon feeding a diet extremely rich in carbohydrates, the relative content of water in the body increases; that of protein and ashes decreases. It can not be decided whether these changes are caused by the excess of carbohydrates or the simultaneous lack of proteins and mineral foodstuffs in the diet.

The inorganic constituents of the food can not be spared at all. The alkaline salts doubtless are most important for maintenance; and an animal dying when fed a salt-free diet or a diet poor in salts will succumb from want of alkalies. A lack of the other minerals can be sustained much longer and easier. For a long time we have argued that the growth in the animal body, like in young plants, will suffer if there is a lack of but one of the necessary mineralic components. An idea which may be compared to the "all or nothing" law for heart contraction has been introduced by v. Bunge as the "law of minimum." If the minimal quantity of but one mineral constituent needed for normal growth should not be supplied by the food, no growth will take place, or growth only so far as normal body tissues can be formed by means of the mineral supply.

This law to a certain extent possibly may be right applied to the alkali salts. So far as the mineral constituents forming the skeleton, calcium, and phosphorus, are concerned, surely the law does not hold true, and probably also not regarding iron.

Experiments in which young animals were fed upon a food poor in calcium or phosphorus showed that in spite of a considerable lack of these minerals, the increase in weight and the growth in general was equal to that of normal animals fed on the same food after addition of calcium or phosphorus. The only effect of a lack of both minerals was certain pathologic changes, principally of the skeletal system. While these processes observed after feeding diets poor in calcium salts resemble mostly those in rickets, Lipschütz and Heubner report that dogs fed on a phosphorus-poor diet show changes of the bones to be compared with those in Barlow's disease.

Chemically these pathologic bones contain less ash, more organic material, and more water than normal ones; the other tissues of the body, with the exception of the brain, usually do not loose calcium or phosphorus.

However, when the phosphorus content is made so low that all cells of the body will suffer a lack of phosphorus, Heubner has observed a kind of cachexia with dogs, most of the animals dying or suffering in their capability to grow. I don't remember experiments in which a diet similarly poor in calcium has been fed.

The form or "binding" of calcium or phosphorus in the foodstuffs, according to most of the recent experiments, seems to be not of great importance. It is quite sure that from organic phosphorus compounds (lecithin) inorganic phosphates can be synthesized and apparently the inorganic phosphates can be used for the production of organic phosphorus compounds as nucleines and phosphatides; thus the body can rely entirely on either organic or inorganic phosphorus in the food.

Insufficient supply of iron causes a diminution of hemoglobin in the blood. Milk being a food exceptionally poor in iron, a too prolonged exclusive milk feeding will cause a relative lack of iron of the growing body, and probably it is quite justifiable to call upon this fact in order to explain certain forms of anemia with babies after a long exclusive milk diet.

There are hardly any experiments made to investigate the effects of feed lacking other mineral constituents than those discussed above. Possibly lack of chlorine, and together with it a lack of alkalies, has to be regarded as cause of these nutritive disorders observed with infants after a long extensive cereal diet and usually designated as "Mehlnährschaden."

Water, a very important food constituent, is taken by young animals in a comparatively much greater quantity than by adults. We are not able to give a reason for this great demand of fluids. The quantity needed to build new body tissues is by no means so great as to explain this high demand of water. In the only experiment made regarding this question, Spiegler has shown that the increase of weight of a dog, the water supply of which was limited, did not reach that of a brother animal fed the same quantity of foodstuffs but which was allowed to drink water besides.

Since Mendel, Osborne, and Röhmann have succeeded in feeding young rats and mice on an artificial mixture of protein, carbohydrates, and salts, and their animals developed normally, it is proven that these constituents of food are sufficient to allow a normal growth of the body, and no others are necessarily demanded. However, these experiments do not prove that other food constituents, as, for instance, the so-called "extractives" may not be of a certain importance for the nutrition of the growing organism. Even disregarding the value of just those substances for the palatability of a diet, from several experiments the impression is obtained that animals fed on artificial mixtures of foodstuffs in but a rare number of cases will flourish and grow like animals fed on mixtures of natural foods. On the other hand, different mixtures of foodstuffs, when equal in their nutritive value according to the usual ideas, do not always give the same effect in feeding experiments. That has been proven clearly

by the detailed experiments of Hart, McCollum, and their collaborators. Calves fed three years on wheat did not develop as well as the control animals fed on rations of oats or corn in quantities of equal nutritive value.

It may be that the character of the proteins here plays an important rôle; it may be that these vegetable foods are lacking in other constituents not known yet or not considered to be of importance; in any event, it must be of great interest to find the reason for these differences.

The influence of the food upon the growing organism has finally been demonstrated alike by the experience gained in both disciplines mostly interested in the growing organism, namely, pediatrics and animal husbandry, and in manifold ways, as well as by critical observations made in practical hygienic studies. It has been proven, above all doubts, that children of the poorer classes in every country are smaller in weight and size than those of the socially better classes. Of course, it would be difficult to show that the differences of nutrition are the sole reason for these variations; however, we will not mistake in regarding the food as an important factor. More convincing are the extensive investigations of McCay, who tried to show that those people of India, who live on a one-sided purely vegetable protein-poor diet, are physically inferior to those races which live under the same conditions, except that they take a mixed food richer in protein. Whoever will make the acquaintance of this country, and its inhabitants will notice how the children of the same people here show a much better physical development than in the European home; and he will be justified in asking if that may not be explained by the more favorable conditions of life, especially regarding food and nutrition.

WEDNESDAY MORNING, SEPTEMBER 25, 1912.

THE ANTAGONISTIC ACTION OF SALTS.

Dr. JACQUES LOEB, Head of the Department of Experimental Biology, Rockefeller Institute for Medical Research, New York City.

1. Since the salts do not furnish any of the energy which is required for the maintenance of life and since they are found in all living organism, the question arises: What is their physiological functions? Researches have made clear one function of salts, namely, that of safeguarding the specific permeability of cells. This function finds its expression in the so-called antagonistic salt action. The cases of antagonistic salt action are so numerous that in the short time at my disposal I shall have to confine myself to a few examples which, however, I think will go far toward an unequivocal explanation of the nature of antagonistic salt action.

The first case of antagonism I intend to discuss is that between acids and salts. The first observation on the antagonism between acids and salts, which I published in 1899, was as follows: A muscle, when put into an isotonic solution of NaCl, to which some HCl has been added, absorbs water and swells. The same is true for a muscle when put into a strong neutral hypertonic solution of NaCl. There is an initial loss of water, which is followed by an excessive absorption of water. If, however, the muscle is put into a strong hypertonic and acid solution, the muscle does not swell at all, but, on the contrary, loses water. The mechanism of this phenomenon was cleared up to a large extent by the experiments of Procter and of Pauli and Handowski on the effect of acid and salt on proteins. Gelatine will swell under the influence of acid alone and under the influence of salt alone, but it will be dehydrated under the combined effect of acid and salt. Pauli and Handowski showed that the influence of acid upon the viscosity of protein solutions can also be inhibited through the addition of salts.

Wasteneys and I demonstrated the existence of this antagonism between acids and neutral salts in the living organism. We selected the marine fish *Fundulus* for our experiments, since it is in wide limits independent of osmotic pressure, and this makes it a favorable subject for these experiments.

We found that in a 3/10000 N HNO_3 solution the fish died within an hour; if, however, the solution contained 20 cubic centimeters m/2

NaCl, the fish could live for days, if not indefinitely. If the HNO_3 solution was more concentrated, more NaCl was needed to counteract the toxic effect of the acid. The same was found in the case of other acids. We tried to ascertain the maximum amount of acid which could be rendered harmless by neutral salts. As salts, we used a mixture of NaCl+KCl+$CaCl_2$ in the usual proportions. We found that, in a m/4 solution of this mixture, the fish was able to resist indefinitely a N/1000 solution of HCl, or any of the strong mineral acids. Without the salt the fish died in less than an hour. If the concentration of the salt is higher than m/4, it proves less effective, though the fish lives naturally in sea water, and can resist a much higher concentration of salt than that contained in sea water. The question presented itself: How does the acid kill the fish and how does the salt prevent this action? When the fish are put into a pure acid solution or into acid solution which does not contain enough salt, the epidermis soon becomes opaque and white and is thrown off in shreds. If a sufficient amount of neutral salt is added this does not take place. Similar changes occur in the gills, and I am inclined to believe that the rapid death of the fish in the acid solution is due to suffocation caused by an injury of the cells of the gills in the acid. The excised gills become rapidly opaque and swell in a 6/10000 N solution of HCl in distilled water. If, however, the 6/10000 N solution is prepared in an m/4 NaCl solution the gills remain normal a long time.

How does the salt prevent the death of the cells of the epithelium and the gills? Here, possibly, the analogy between the observations on muscle or gelatine gives the explanation. If we assume that the surface of the epithelial cells contains a layer of a protein which acts like gelatine, this protein will swell in the presence of acid alone or of acid and too little salt. This swelling will allow the acid to diffuse into the cell and thus cause its death. If, however, a sufficient quantity of neutral salt is present, the protein at the surface of the cells is dehydrated and thereby rendered comparatively impermeable for the acid, and the life of the cell is saved.

2. This summer I found a method by which this idea could be tested. The experiments were made on the fertilized eggs of *Fundulus*, which develop in sea water, but can develop also in distilled water. These eggs have a tough membrane, inside of which the yolk sac with the embryo is contained. The egg membrane is not connected with the embryo. Like the adult fish itself, the embryo is killed very rapidly in an acid solution, but, in the presence of a neutral salt, the acid fails to kill the embryo.

These eggs have a higher specific gravity than sea water. In a 11/8 m NaCl solution they will sink, while in a 12/8 m NaCl solution they will float. When these eggs are put into a mixture of 50 cubic centimeters 3 m NaCl+1 cubic centimeter 2 1/2m $CaCl_2$, they will

float on top of such a solution for three days or more. After that they sink. Observations show that the sinking is preceded by a gradual shrinking of the yolk sac of the embryo. The fact that this shrinking occurs so late indicates that the egg membrane is practically impermeable to water and salts. Such a conclusion is supported by the fact already mentioned: that the eggs will develop in distilled water as well as in sea water, or in sea water of twice its normal concentration.

Eggs of *Fundulus* were put into an acid solution, e. g., N/333 solution of acetic acid. After 17 minutes, the eggs were taken out of the solution, and their surface was freed from every trace of acid by repeated washing in sea water. Some remained in sea water and developed perfectly normally, showing that the short acid treatment had not injured the embryo. Others were put into the mixture of 50 cubic centimeters 3 m NaCl+1 cubic centimeter 2 1/2m $CaCl_2$ (which will be designated briefly as the "test solution"). The eggs floated at first, but sunk to the bottom in less than seven hours. Eggs not treated with the acid floated for three days or more. The acid treatment, which had not affected the embryo, had, however, increased the permeability of the egg membrane to water (and possibly to a slight extent to salts) at least ten times.

At the same time, another lot of the eggs were put into a N/333 solution of acetic acid in a m/2 solution of NaCl+KCl+$CaCl_2$. When these eggs were put after 25 minutes into the test solution, they were all still afloat after 22 hours, and some were even afloat after two days. Even when the eggs were left in the mixture of acid and salt for over three hours, they had not suffered more than when they remained only 25 minutes. The addition of the salt, therefore, inhibits the increase of permeability of the membrane which the acid alone produces.

One consequence of this is that the acid itself is prevented from entering into and killing the embryo or the protoplasm of the epithelial cell.

There is still a better test for the correctness of this view. It has been found by various authors that the dehydrating action of the various acids on gelatine or muscle is not the same, and is apparently a maixmum for H_2SO_4. I asked Dr. Beutner to ascertain the minimum of salt needed to cause dehydration of the muscle for a given concentration of an acid. He found that the system sulphuric acid—sodium sulphate had the maximal dehydrating efficiency among all the systems tested.

If our theory of the cause of the antagonism between acid and salt is correct, namely, that it is due to hydrating effect of the acid alone and a dehydrating effect of the combination acid salt, it should be easier to counteract the influence of sulphuric acid by

Na_2SO_4, than to counteract the influence of HCl by NaCl. It was found that this is indeed true.

Eggs were put into a mixture of 0.4 cubic centimeters N/10 HCl+50 cubic centimeters H_2O and taken out at various intervals. When taken out after 21 minutes and put into the test solution they sank to the bottom in less than 2½ hours. Eggs that had been treated for 20 minutes with an HCl solution of the same strength, but made up in a m/2 solution of NaCl+KCl+$CaCl_2$, instead of with H_2O, floated in the test solution more than 4, but less than 22 hours. There was then a distinct antagonistic effect between the salt and the acid, but it was not complete. The eggs should have floated on the test solution more than three days if the antagonism had been complete. A 6/5000 N solution of HCl could not be antagonized at all by a m/2 salt solution.

It was found that H_2SO_4 increases the permeability of the eggs almost as quickly as an HCl solution of the same concentration. Eggs that had been in 0.4 cubic centometer N/10 H_2SO_4+50 cubic centimeters H_2O sank to the bottom in the test solution in less than 3½ hours. When the eggs were treated in a mixture of 0.4 cubic centimeters N/10 H_2SO_4+50 cubic centimeters m/2 Na_2SO_4 for 20 minutes and then put into the test solution, some of them were still afloat after three days. In this case the antagonism was complete. The following fact is still more instructive. While in the system HCl—m/2 NaCl it was no longer possible to annihilate the toxic effects of a higher than a 4/5000 N HCl solution, in the system H_2SO_4—m/2 Na_2SO_4, an antagonization of more than twice that concentration of acid was still possible.

These facts leave no doubt that the antagonism between acids and salts consists in a maintenance of the impermeability of the membrane of the egg to water and salt which the acid alone destroys; and, second, that the increase of the permeability by the acid and its antagonization by salt is due to a common action of both upon a protein.

This latter fact is of fundamental importance in regard to the nature of the substances upon which the semipermeability of the cell depends. It is assumed by many authors that the specific semipermeability of living cells is due to lipoids. But the above-mentioned observations leave no doubt that the substance upon which the permeability or impermeability for acids or salts depends is a protein.

3. Thirteen years ago I introduced the term "physiologically balanced salt solutions" for such solutions in which the various constituents were in a condition of complete mutual antagonization. The model of such a solution is the mixture of NaCl+KCl+$CaCl_2$, in the proportion in which these three salts exist in the ocean. It is not gen-

erally realized to what extent antagonistic action takes place in this solution. In order to find this out we must experiment on organisms which are independent of osmotic pressure such as *Fundulus* and not on nerves or muscles which demand a definite osmotic pressure. Years ago I showed that these fish can not live in a pure NaCl solution of the concentration in which this salt is contained in the sea water (m/2), but that they can live in such a solution indefinitely if KCl or $CaCl_2$ is added. KCl and $CaCl_2$ are not required by the fish directly, because in a weak NaCl solution, e. g., m/32 or m/16 or in distilled water they can live indefinitely without KCl or $CaCl_2$. These two substances are only needed to counteract the deleterious effects of a pure NaCl solution of high enough concentration. What was shown for NaCl could also be shown for KCl. The KCl in the concentration in which this substance is contained in the sea water (about m/100) kills *Fundulus* in a few days, if it is alone in solution. This is purely due to the specific toxic action of the KCl, since a pure m/100 NaCl solution is perfectly harmless for the fish. I found two years ago that the toxic action of the KCl is inhibited if we add a certain amount of NaCl to the solution, namely, 17 molecules of NaCl for one molecule of KCl.

It was assumed that the toxic action of NaCl, if alone in solution, consisted in this, that it increased the permeability of the membrane of the fish whereby NaCl could enter; while the addition of KCl and $CaCl_2$ counteracted this effect and maintained the normal degree of impermeability of the membranes of the cells. In the same way we may conclude that the addition of NaCl to KCl inhibits or retards the diffusion of KCl into the fish.

Ten years ago I had found that the eggs of *Fundulus* die comparatively rapidly, if put immediately after fertilization into a pure 5/8 m NaCl solution, while they live and develop if a trace of a salt with a bivalent metal, e. g., $MgCl_2$, $CaCl_2$, $SrCl_2$, or $BaCl_2$ is added. It can easily be shown that in these cases also the antagonistic salt action is due purely to the inhibition of the increase in permeability which the 5/8 m NaCl would produce if it were alone in solution. If we put fertilized eggs of *Fundulus* into a 3 m solution of NaCl, they float, since their specific gravity is considerably less than that of the solution. In less than three hours, however, their yolk sac begins to shrink, the egg membrane collapses, the embryo dies, and the eggs sink to the bottom of the solution.

The same occurs, only much more rapidly, if the eggs are put into a 10/8 m solution of $CaCl_2$, or $MgCl_2$, or $SrCl_2$, or $BaCl_2$.

If we prepare a mixture of 50 cubic centimeters 3 m NaCl + 2 cubic centimeters 10/8 m $CaCl_2$, the eggs will float on top of such a solution for three days or more. If we substitute $SrCl_2$ for $CaCl_2$ the result is the same. The addition of $MgCl_2$ or $BaCl_2$ to a 3 m NaCl

solution has the same effect, only that the eggs will not float quite as long on top of the solution. The experiment is still more striking if we use a mixture of NaCl + KCl + $CaCl_2$. I have seen the eggs float on the surface of a 2 1/2 m solution of NaCl+KCl+$CaCl_2$, for 11 days, and during all that time the yolk sac hardly shrank, and the embryo kept alive; while eggs of the same culture sank in a pure 2 1/2 m solution in less than three hours.

The explanation of these experiments is simple. The egg membrane of *Fundulus* is practically impermeable for water, and this explains why the eggs do not shrink, but continue to develop in a 3 m balanced solution. If we put them, however, into a pure 3 m NaCl solution, the NaCl alters the membrane and renders it more permeable. The consequence is that the normally inpermeable membrane becomes now permeable for water and slightly permeable for salts. As a consequence the egg loses water, its specific gravity is increased, and it sinks. If we put it into a mixture of 3 m NaCl+10/8 m $CaCl_2$, the latter prevents the increase of permeability which the 3 m NaCl would produce if it were alone in solution.

The correctness of this interpretation is proved by the following experiments: When we put the fertilized eggs of *Fundulus* into a 10/8 m solution of $CaCl_2$ for only four minutes and then put them back into sea water they will continue to develop normally. If, however, we put them into the test solution, where they should float for three days or more, they will sink in less than 1½ hours. This shows that the short treatment with a $CaCl_2$ solution had no other effect but to increase the permeability of the egg membrane.

In a similar way it can be shown that a 3 m NaCl solution increases the permeability of the egg membrane long before it injures the embryo or causes the egg to sink. If we put eggs of *Fundulus* for an hour into a 3 m NaCl solution, they are to all appearances normal. Yet, if we put them into the test solution, they will sink in less than five hours.

In this way we can prove that the treatment of the eggs with a nonbalanced injurious salt solution causes primarily an increase in the permeability of the membrane. The antagonistic action by a second salt consists in the inhibition of this effect.

Osterhout's experiments.

4. The increase in permeability caused by acids or salts is reversible. If the eggs are put for 40 minutes into a 4/5000 N H_2SO_4 solution, their permeability is much increased, and they sink in the test solution in less than two hours. If they are put into sea water, their normal impermeability is restored in four hours. After a treatment with an equally concentrated solution of HCl, it takes still longer until the normal impermeability is restored. The same reversibility of the

effects of a $CaCl_2$ solution or NaCl solution upon the permeability of the membrane can be observed.

I studied the conditions for this recovery and found that this also is due to an action of salts. If the eggs are treated for 40 minutes with a 4/5000 N solution of HCl or H_2SO_4, they will recover completely, after some time, if put into sea water or a neutral m/2 solution of NaCl+KCl+$CaCl_2$. If they are put into distilled water, the eggs will continue to live and the embryos will hatch, but their natural impermeability will not be restored. If they are put at any time into the test solution, they will sink in a few hours, no matter how long they remain in the distilled water.

We can, therefore, summarize the results of these experiments, as well as of many others, by the statement that the antagonistic action of salts is due, in all cases where an analysis of these phenomena is possible, to a prevention of the increase in permeability which a salt would have if it were alone in solution. The fact that these injurious effects are reversible indicates that the changes in permeability may play a great rôle in the physiology and pathology of cells, a fact to which Osterhout has also called attention. The experiments show that the salts are responsible for the reversibility of the increase in permeability. It is also of importance that these experiments seem to prove that the antagonistic action of acids and salts, and possibly of electrolytes in general, is due to an action upon proteins.

THE RÔLE OF SURFACE TENSION IN DETERMINING THE DISTRIBUTION OF SALTS IN LIVING MATTER.

A. B. Macallum, M. B., Sc. D., F. R. S., Professor of Biochemistry in the University of Toronto.

The distribution of salts in living matter is, in the current conception of physiology, supposed to be governed by the ordinary forces that determine the distribution of substances dissolved in a simple voluminous fluid. These forces, apart from the solvent action of the fluid, are the same as those which effect the distribution of the molecules of a gas in the space which it occupies. The substances dissolved are thus conceived to be in that state of rarefaction which would put them each in the state of a gas, compressed or confined by the boundaries of the solution, just as a gas is confined by the walls of the containing vessel. Each solute then is in a state in which the gas laws apply. If the solute is a simple nonelectrolyte—that is, does not serve as a conductor for electricity in the solution—the pressure its molecules exert as a gas is in proportion to its molecular concentration. If, on the other hand, the solute is a conductor and the solvent is water, few, more, or many of its molecules are dis-

sociated, each one of the resulting dissociated parts, the ions, acts as a molecule acts, and in consequence the pressure the solute exerts is in proportion not to the molecular concentration but to the number of the ions and the molecules undissociated.

This pressure derived from the molecules of the solute is called the osmotic pressure because it is supposed to be the force that is concerned in the exchange of solvent and solution through a permeable membrane or of pure solvent through a semipermeable membrane. Osmosis is, on this conception of the nature of a solution, a series of phenomena the causation of which is due to the operation, in the last analysis, of gas laws. The ultimate effect of the operation of this force is the equalization of pressure not only throughout the solution but also on both sides of the membrane. In no case should the derived pressure on one side of a membrane rise to a degree higher than its source on the other side of the membrane.

In recalling these familiar points in the current theory of osmosis, the motive is to prepare for a clearer conception of the forces that are fundamentally involved in the distribution of salts in the cells and tissues of the living organism. It is not of course intended at the present moment to question the validity of the hypotheses that are at the foundation of the accepted theory of osmosis. This theory appears to be supported by such a large number of observations and results, derived from experiments devised for the purpose of investigating osmotic phenomena, that it is regarded by many chemists, physicists, and even physiologists as securely established on the bedrock of fact. It is, nevertheless, not to be assumed that the evidence in its favor is absolutely overwhelming, for even the most enthusiastic among its exponents would not claim that there are no facts which run counter to it. It is not, however, the aim of the writer to discuss these or to deny the usefulness of the theory in its application in purely physical or chemical conditions. His concern is rather to call attention to its inadequacy in explaining physiological osmosis or exchange through living membranes, tissues, and cells.

When the van 't Hoff-Arrhenius theory was first advanced, it was welcomed by physiologists with acclaim, because it appeared to furnish a complete explanation of the phenomena of secretion, absorption, and of the processes involved in the exchange between blood and lymph and between lymph and cell contents. It was not regarded as possible that there should be a great gulf fixed between physiological osmosis and physical osmosis, and evidence of a close relation between the two, of indeed their complete identity, was eagerly sought on all hands. Now, after twenty years, the physiologist is in a position to say how far those hopes have been met, and the outcome is an attitude of dissatisfaction. Not only have the phenomena of osmosis in living

tissues not been explained on the basis of the theory, but there are facts which seem to contradict it completely. The phenomena of secretion and absorption in general are not rendered more intelligible with its aid, and it gives us no assistance whatever in some cardinal difficulties. There is, for instance, renal secretion. In this the osmotic pressure should not exceed the osmotic pressure of the blood or lymph, and yet the urine may have an osmotic pressure in excess of that of the blood or lymph up to as much as five or six times the latter. Here indeed the derived pressure rises higher than its head or source. This fact is not only irreconcilable with the van 't Hoff-Arrhenius theory, but it seems to contradict the second law of thermodynamics. Maxwell did, indeed, postulate that it was possible for energy to pass from a system where it was low to one where it was high, but he invoked for this purpose the aid of microscopic or, shall I say, ultramicroscopic demons, to sort and separate out with the aid of shutters the molecules endowed with a high energy from those having only a low energy or velocity. The facts of renal excretion have driven some physiologists back to that explanation. The structures that are involved in this excretion are minute microscopic elements, cells which appear to permit solutes to pass freely through them from the blood and lymph into the urine, but not to return from the urine into the blood or lymph. The cells thus act as the demons and the shutters in Maxwell's system, for what else is signified in the supposition that a vital force is involved in the separation of a urine of high concentration?

It is necessary, therefore, to turn to some other explanation for assistance in our efforts to understand what is involved in physiological osmosis. The mistake made in the application of the current theory of osmosis is that it postulated in physiological systems only those conditions which are supposed to obtain in a system of two fluids, one a solution and the other the pure solvent, separated by a membrane which has no other property except that of being permeable to the molecules of the solvent. Such a membrane does not exist, nor can it be made. Even the cupric ferrocyanide membrane used by Pfeffer, by which he obtained, in the case of sugar solutions, the results which constituted a signal foundation for the van 't Hoff Arrhenius gas theory of solutions can not now be regarded as answering the conditions demanded by the theory.

One of the factors neglected in all such theories of osmosis was surface tension. It was not, however, left wholly out of consideration, for Poisson[1] 85 years ago advanced the view that capillarity, acting through the pores of a dialyzing membrane, determined the direction and the volume of the flow or exchange through the membrane from one fluid to the other. Nevertheless, all the subsequent

work till within 10 years ago, when Traube's crusade against the currently accepted theory began, almost completely ignored surface tension.

The neglect of surface tension as a factor entailed more striking effects in physiological osmosis than in purely physical examples of osmosis. Physiological membrances are constituted of cells, and these present, on their interior as well as on their exterior, interfaces of enormously large areal value as compared with the areal value of the surface of a simple physical membrane of homogeneous constitution. On all these interfaces surface tension plays its part. Further, the cytoplasm of each cell represents a mixture of two phases, one protein-water, the other water-protein, the former of which exists, in all probability, in the form of discrete particles, dispersoids, as they may be termed, of ultramicroscopic size, each of which, in contact with the other phase, the water-protein medium, presents an interface where the force of surface tension operates in a greater or less degree than on the surface of the cytoplasm as a whole. There are, besides, the vacuoles, granules, and other cellular inclusions, all of which postulate the occurrence of interfaces where surface tension acts.

What this means in a general way may be made clear by a simple illustration. If a solution of potassium permanganate, or some other salt giving a colored solution, be allowed to trickle through a layer of sand of, say, a couple of feet in thickness, the fluid which first issues may be completely colorless, owing to the operation of surface tension on the interface formed by each sand particle in contact with the solution. The molecules of the dissolved potassium permanganate are condensed on the surface of each particle and held there, and the fluid that passes on, bathing the surfaces of successive sand particles, becomes less and less concentrated, until finally it attains the stage of infinite dilution, when it appears colorless. This condensation is a surface tension effect due to the action of the Gibbs-Thomson principle of surface condensation. The sand particles are themselves inert, the solution does not penetrate into their interiors, and neither the solvent nor the solute enters into chemical combination with the silica constituting the particles. The resulting condensation is therefore a purely physical effect.

Now if we suppose the particles to be replaced by living cells, each, unlike the sand particles, of microscopic size, there will be not only an increase of interfacial area, where condensation may take place, but also a penetration of the cells by the solution, and in consequence the solute or solutes which enter the cells may undergo therein an unequal distribution through the operation of the Gibbs-Thomson principle. This latter should, on a priori grounds, be re-

garded as an all-important factor in determining diffusion through cells.

The theoretical reasons for assuming the Gibbs-Thomson principle to be of such importance in osmosis are fortified by facts. These latter are the results of purely physical investigations on surface tension condensations as well as of observations in microchemistry, furnishing ocular demonstrations of the occurrence of such condensations in living cells. To understand fully the bearing of these it is necessary to enter into an explanation of some of the elementary points involved, and the first to be thus treated is the Gibbs-Thomson principle.

This principle involves the fundamental fact that if a substance dissolved in a fluid system (e. g., a drop of water) increases the surface tension of the latter, it is less concentrated in the surface than elsewhere in the system, while a substance which lowers the surface tension is more concentrated in the surface. The surface tension of the system may be lowered over the whole or a part of the system by putting it in contact with other surfaces, fluid or solid, and a diminution of surface tension takes place when solids or other fluid systems are introduced into its interior, the diminution obtaining on the interfaces where the fluid comes in contact with the solids or with the introduced fluid systems. Thus the surface tension of water at its contact with sand particles or with spherules of oil or other immiscible fluids is reduced.

Now wherever surface tension is reduced, as in the illustration cited, the solute or solutes are condensed, whether they tend under other conditions to raise or lower surface tension. This explains the condensation of potassium permanganate on the surface of the sand particles. The degree of condensation, or, in the case of increase of surface tension, of a diminution of concentration at an air-fluid surface, depends on the extent of the diminution or increase of surface tension, as well as on the concentration of the solute throughout the system, but, assuming the application of the gas laws to dilute solutions, the concentration as deduced from Gibbs's formula would be:

$$S = -\frac{C}{iRT} \cdot \frac{d\sigma}{dC}$$

Where S is the surface excess or deficiency per unit of surface area of the part affected, C, the concentration throughout the fluid, σ, the surface tension value per centimeter, iR the gas constant, and T the absolute temperature.

The value of S, as experimentally ascertained, except in certain determinations made within the last three years, was very small, and these ranged from a deficit of 0.024 milligram per square meter of

surface in normal solution of sodium chloride to an excess of 0.4 milligram of sodium oleate per square meter in a $\frac{N}{500}$ solution of that soap. These values, if they were the only ones accessible, would make surface concentration a negligible factor in fluid systems, except for problems of very limited theoretical interest, but the results of Lewis's determinations of surface concentration at aqueous solution-oil interfaces and at aqueous solution-mercury interfaces give surface concentration a value which is of surpassing interest in the explanation of a large number of physical and physiological problems. For the proper appreciation of those determinations the reader must consult Lewis's papers. There is opportunity here only for a brief indication of them. In a 0.25 per cent solution of sodium glycocholate the concentration at the interfaces formed with droplets of hydrocarbon oil was 70 times the theoretic value, and, at interfaces formed with droplets of mercury, it was 25 times the theoretical value. In a sodium oleate solution the concentration at the solution-oil interface was about 100 times the value given by Gibbs's equation. With solutions of sodium hydrate, Congo red, and methyl orange the concentrations, as experimentally ascertained, were respectively 43, 25, and 20 times the theoretic value. In the case of inorganic solutes the quantity adsorbed exceeded the theoretic amount, but it was chiefly the cation that was so affected. With silver nitrate, the silver adsorbed was 5 times in excess; with cupric chloride, the copper was 17; and with potassium chloride, the potassium was more than 30 times the value calculated from the equation. The excess of the cation is, in Lewis's opinion, probably due to electrical effects, since the oil used was negatively charged and the potential difference between the oil and water was approximately 0.05 volt. The great excess of amount adsorbed in the case of each organic compound could only be explained, according to Lewis, by supposing that the adsorbed material is in a gelatinized or colloidal condition on the surfaces of the droplets of oil or mercury.

Even when considerable allowance is made for experimental errors in Lewis's results, the concentrations found by him are of such a magnitude as to claim attention by physiologists and biochemists. Taken in conjunction with a number of facts which I have observed in my microchemical studies, they make it imperatively necessary to revise our views, not only as to the manner in which salts are distributed in living cells, but also as to the primary factor concerned in physiological osmosis. Interfacial surfaces exist in living cells and also on their surfaces in tissues, and, on a priori grounds, the tensions on these interfaces should determine, because of the relatively great areal value of these interfaces, the distribution of the solutes in the cells and about them.

The clearest evidence that this is the case is supplied by my own microchemical studies on the distribution of potassium salts in cells and tissues. By means of the cobalt sodium hexanitrite reagent for potassium, used as I have elsewhere indicated, it is possible to demonstrate under the microscope presence of potassium when it is in a concentration almost, or approximately, as low as 1 in 1,000,000 As the reaction which precipitates the potassium is instantaneous in character it may be relied upon to indicate the localization in living matter of potassium salts. A number of precautions must, of course, be observed in its use on living tissues, one of which must be that the reagent shall get immediate access to the structures in which the localization of potassium is to be investigated. For this purpose the tissues must be rapidly frozen with a CO_2 spray while they are still fresh and sections prepared of not thicker than 20μ, which must be allowed to enter the reagent while still frozen. The reagent penetrates all parts of such sections immediately and precipitates the potassium wherever it occurs, and its distribution may, after appropriate treatment, be determined under the microscope.

In the case of isolated cells, whether derived by teasing from tissues or of protozoan or protophytan forms, the reagent may be directly applied. Here the reagent penetrates each cell rapidly and localizes the potassium salt.

The results of the application of this method show that condensation, on interfaces and in surfaces where the tension is low, is a distinct factor in determining the distribution of salts in tissues and cells. On the external surfaces of pancreatic and salivary tubules, and on the external surfaces of those convoluted tubules that were active in excretion when the kidney from which the preparations were made were removed, marked condensations were found, corresponding in position with the interfaces formed by the lymph in contact with the external ends of the gland cells. In nerve tissue potassium forms a similar deposit about the nerve and ganglion cells at the lymph-nerve cell interfaces.

Inside of cells, potassium forms condensation layers on the surfaces next to the lumen in each secreting pancreatic and submaxillary cell, and in the cells of active convoluted tubules in the kidney. The occurrence of these condensation layers next to the lumina indicate very clearly that the lumen surfaces of such secreting cells are under lower surface tension than either the lateral or external surfaces of the same cells during their activity, that is, their secreting or excreting phase. It may, indeed, from present evidence, be advanced as a general law that in the actively secreting or excreting cell the secreting surface has always a surface tension lower than that of any other surface and especially than that of the surface at the opposite pole of the cell. It may also be stated as a general fact that in pancreatic

and salivary cells in active secretion, and in cells of the actively excreting convoluted tubules of the kidney, apart from the condensation layers referred to, the cytoplasm gives no indication of the presence of potassium. In other words, though the condensation layers of potassium may indicate a high degree of concentration of potassium, yet the cytoplasm elsewhere may contain not more than 1 part in 1,000,000. It is evident, therefore, that when potassium salts enter such cells they are swept at once to the surface of low-surface tension. Surface tension, accordingly, dominates the distribution of potassium salts in secreting and excreting cells.

It dominates it also in nerve cells. The axon of a nerve cell, as well as its dendrites, exists only because the surface tension of the superficial film of the axon and of each dendrite is less than that of the surface of the body of the cell. Now the only potassium found in a nerve cell obtains in the superficial portion of each axon; that is, surface condensation occurs here also. Whether there is a condensation in the superficial film of each dendrite can not be determined, chiefly because of the difficulty in localizing it there under the microsope. The quantity in the cytoplasm of the nerve cell itself must be at most only 1 in 1,000,000. Consequently, when potassium salt penetrates a nerve cell, it must be swept to the region of low-surface tension.

In striated muscle fiber the distribution of potassium wholly at the two extremities of each sarcous disk, while the muscle is uncontracted, and the tendency it shows to diffuse uniformly throughout the sarcous disk when the muscle begins to construct, can only be explained on the supposition that surface tension is the determining factor in this distribution.

In the cells of other tissues potassium is localized, not diffusely, but in points and masses in the cytoplasm, in such a manner as to compel a resort to surface tension as a factor by way of explanation. In the cells of vegetable tissues this is also the case. In not a few instances, in vegetable forms also, in which prolongations of cells occur, to be accounted for only as due to the production of low surface tension at the points where the prolongation occurs, there is a condensation layer of potassium under and in the surface where the prolongation develops. This is specially the case in conjugating *Spirogyra*, *Mesocarpus*, and *Zygnema*, and in primary root hairs of the spores of *Equisetum arvense*. In these forms, under other conditions, the potassium is always localized, not indeed so strikingly as in the conjugating forms, in single superficial condensation deposits, but yet in such a manner as to suggest the explanation that surface tension is the casual factor.

Perhaps the most striking and convincing demonstration of the action of surface tension in determining the distribution of potassium

salts in a living cell is to be obtained in marine species of *Acineta*. The *Acinetæ* are Suctorian Protozoa, in adult condition stalked and sessile, and obtaining their food through tentacles which are extended from two hillocks on the anterior surface of the cell. These tentacles are extended only when the organism seeks food or is absorbing food from its prey. In the cytoplasm are usually a large number of spherules of food matter, chiefly composed of protein, each of which lies separate and in a cavity of its own. There is also the reproductive excretory cavity, into which grows the bud of the cytoplasm, by which reproduction takes place. The extension of the tentacles is undoubtedly due to low surface tension at points on the hillocks where they arise, as well as on the surface of the shaft, and the capitate end of each tentacle when extended. There is also low surface tension at the interface between each spherule and the inclosing cytoplasm, and at the cytoplasm-germbud interface. If now potassium salts occur in *Acinetæ* they should be found in condensation layers in the surface films of the tentacles and on the cytoplasm spherule and the cytoplasm-germbud interfaces, and very little, if any, in the cytoplasm generally.

This is what has been actually found. In the superficial film of each extended tentacle there is an extraordinarily dense concentration of potassium, a less marked but still very distinct condensation at the cytoplasm-germbud interface, and usually a very much less distinct condensation at each cytoplasm-spherule interface, while the cytoplasm generally gives no reaction for potassium, a fact which would indicate a concentration of potassium salt, generally diffused, of about or less than 1 in 1,000,000. When the surface tension in the tentacles rises, and they begin to retract, then the potassium salt of their superficial condensation layers begins to diffuse into the cytoplasm, first into the cytoplasm immediately under the hillocks, and later and gradually into the rest of the cytoplasm. When the tentacles have completely retracted the greater part of the potassium salt they contained is now being distributed throughout the cytoplasm, chiefly or almost wholly, however, on the cytoplasm-spherule interfaces and on the cytoplasm-germbud interface. Eventually, so long as the tentacles are withdrawn, the whole of the potassium present—that is, all that can be demonstrated—is found condensed on these interfaces.

All the phenomena involved in the distribution of potassium salts in *Acineta*, therefore, leave no doubt that the causal factor in this distribution is surface tension. There is, however, more to be learned from the facts observed in connection with this distribution.

When the tentacles are extended the potassium condensation in their surface films is greater than it is in the sea water of the habitat of the *Acinetae* investigated. A high concentration of potassium in

the surface films, a lower one in the sea water, and a concentration in the cytoplasm, generally so low that it does not much, if at all, exceed 1 in 1,000,000, are all facts indicating that surface tension is a dominant factor in osmosis as well as in the distribution of salts in living cells. The potassium in the surface films of the tentacles does not diffuse into the sea water, nor does the potassium of the sea water diffuse through the surface film any more than it diffuses from the surface films into the subjacent cytoplasm, for then there would be equality of concentration within and without the cell. This impermeability of the surface films to potassium salts from without can not be due to lipoids, for then potassium salts would not penetrate the surface films from the cytoplasm below to condense in them. The force that condenses the potassium salts in the films prevents it diffusing in either direction so long as that force operates. Surface tension may then play its part in regulating exchange across interfaces such as are found in physiological membranes.

This brings us back to the cardinal difficulty encountered in attempts to explain physiological osmosis on the basis of the van 't Hoff-Arrhenius theory of solutions. It was pointed out that this theory did not enable us to comprehend how the kidney could excrete a fluid of greater osmotic concentration than that of the blood plasma itself. With the assistance of the concepts regarding surface tension that have been advanced above we are in a position to understand the processes involved fully.

As pointed out above, potassium salts are condensed on the external surface as well as in the lumen surface of each actively excreting cell of a convoluted tubule. The condensations at both points may be very marked, while the general cytoplasm of the same cell may give little evidence of the presence of potassium. Now, it is evident that all potassium salt or salts which enter the external face of such a cell would be swept through the cell by the force of surface tension to the lumen border. Here it may be condensed in a very large quantity, but it is exposed to the action of the stream passing down the lumen from the glomerulus. This stream is generally supposed, *pace* the Ludwig theory, to be more or less pure water. On one side of the lumen interface there is water, or a very dilute solution of salts; on the other, a concentrated potassium condensation. The passage of water into the cell would not dislocate the potassium salts from their condensation layer so long as the difference in surface tension between the lumen surface and external surface is maintained. The only direction the potassium salts could pass would be into the lumen, and this would be facilitated, if the surface tension were not too low, as, for example, it must be in the tentacles of *Acineta*. The stream of fluid in the channel of the convoluted tubule would thus become more and more concentrated as it proceeded downward, and thus it would

have a richer concentration in potassium salts than the blood plasma itself.

If now the other salts of the blood plasma and the organic substances, urea and uric acid, are condensed in some measure, as they probably are, on the same surfaces with the potassium salts, they also would become more and more concentrated in the glomerular stream as it passes down the convoluted tubules, until, finally, it has a greater concentration of these solutes than the blood plasma has Thus would arise the high osmotic pressure of the urine.

To maintain a difference of surface tension between the two surfaces, lumen and external, which would provide for such an excretion, energy must be expended. That the kidney does use up energy is shown by Barcroft and Brodie, who found that, as measured by the oxygen consumed, the kidney liberates about 220 times as much energy as was required in the osmotic concentration of urine. This energy, one can conceive, may be spent wholly or partially in the development and maintenance of the difference of surface tension postulated above.

It may be asked, if osmotic concentration is thus due to surface tension, why the concentration of every solute in the urine should not be the same multiple of the concentration of the same solute in the blood plasma. If the same multiple obtained in each case, as, for instance, 2, then the urine would have twice the concentration of sodium, of potassium, of urea, found in the blood, whereas the actual multiple varies widely in the case of each solute and for any sample of urine.

To answer this question briefly, it is only necessary to say that Lewis's observations seem to show that the degree of condensation varies for each particular compound; that, for example, with sodium oleate it is 100 times the amount demanded by Gibbs's equation, while with potassium it is 30 times. No determinations have been made for sodium chloride, calcium, and magnesium salts, or for urea, uric acid, or other waste metabolites found in urine, but it is permissible to suppose that degree of condensation varies with each, and thus the concentration in the urine would not be a product of a constant and the concentration in the plasma. This, also, will explain the variation in the concentration of the urine from hour to hour.

One other point may be developed out of this subject. Analyses of the kidney, pancreas, liver, salivary glands, and the brain show that the amount of potassium present is approximately equal to, if not in excess of, that of the sodium, while in the blood palsma the potassium is only 6 to 7 per cent of the sodium. Now, as pointed out above, the potassium in the kidney, pancreas, and salivary glands, is largely condensed at interfaces, while in nerve tissue it is present chiefly in nerve cell-lymph interfaces and in the surface films of

the axons. This suggests that the discrepancy between sodium and potassium in the blood plasma, on the one hand, and the organs referred to, depends upon, or is caused by, difference between these two elements in the degree in which they condense at interfaces. A degree of condensation for potassium in its salts, considerably higher than for sodium in its salts, would tend to make the amounts of the two in the tissues nearly equal and thus account for the amounts of these two found in the analyses.

I must now conclude, and as briefly as possible, in again directing attention to the central points of this contribution. From all the foregoing observations, it may be gathered how far surface tension is a factor in determining the distribution and localization of salts in the fluids and tissues of the body. The forces governing the distribution of salts in ordinary solutions are profoundly modified in tissues and organs by the action of surface tension, which, as explained above, is a very important factor in the processes of secretion and excretion. The part this force plays in determining the inorganic composition of the tissues and in influencing the functions of the organs, accordingly, justifies the emphasis which I have sought to give it in this address.

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[1]Ann. de Chim. et de Physique, 1827, XXXV, 98.

UEBER DIE ROLLE DES KOCHSALZES UND DES WASSERS IN DER ERNÄHRUNG DES MENSCHEN.

Dr. HERMANN STRAUSS, Professor of Clinical Medicine, University of Berlin, Germany.

Das Kochsalz hat erst in den letzten Jahrzehnten in der menschlichen Pathologie diejenige Beachtung gefunden, welche seiner Bedeutung für die Physiologie entspricht. Das fällt auf, wenn man bedenkt, dass das Kochsalz das Salz *κατ' ἐξοχήν* ist, das speziell für die Regulierung der osmotischen Spannungen im Organismus in besonderem Grade Verwendung findet. Wir danken es vorzugsweise den physikalisch-chemischen Forschungen, dass unser Interesse für die Bedeutung des Kochsalzes auch in der Pathologie geweckt worden ist, und es sind die Forschungsergebnisse auf dem Gebiete der Pathologie im Laufe der letzten 10 Jahre derartig geworden, dass sie—was man nicht selten beobachten kann—auch für die Physiologie nach zahlreichen Richtungen hin anregend und klärend gewirkt haben. Wenn ich in Folgendem, einer mich ehrenden Aufforderung folgend, ein Referat über die Bedeutung des Kochsalzes und des Wassers für die Ernährung des Menschen erstatte, glaube ich schon

aus dem soeben genannten Grunde die aus den Forschungen der Pathologie gewonnenen Gesichtspunkte etwas in den Vordergrund rücken zu dürfen. Eine solche Erlaubnis möchte ich mir aber auch aus dem Grunde hier erbitten, weil meine eigenen Forschungen über die Stellung des Kochsalzes und des Wassers, soweit ich diese hier als Grundlage zur Beurteilung der folgenden Fragen benutzen will, vorzugsweise an Kranken angestellt sind. Da sich mein Beobachtungsmaterial vorwiegend auf Erwachsene erstreckt, so bitte ich mir auch zu gestatten, mich hier mit den einschlägigen Verhältnissen bei den Erwachsenen mehr als mit denjenigen im Kindesalter zu beschäftigen. Die Absicht, kurz zu sein, veranlasst mich leider auch, auf eine erschöpfende Darstellung aller für die vorliegenden Fragen wichtiger Punkte zu verzichten. Bei der Auswahl der einzelnen Punkte hielt ich es ganz allgemein für richtig, Fragen des Salzstoffwechsels hier ausführlicher zu betrachten als Fragen des Wasserstoffwechsels, weil die jüngste Zeit—wenigstens in der Pathologie—auf dem vorliegenden Gebiet mehr Neues gebracht hat, wie auf dem letzteren.

Von den uns hier interessierenden Tatsachen ist die wichtigste die schon längst gemachte Feststellung, dass der menschliche Organismus mit ganz enormer Zähigkeit die prozentuale Konzentration des Blutes und der Gewebssäfte an Kochsalz festhält. Dies wird durch eine sehr scharfe Bilancierung zwischen Ausgabe und Einnahme erreicht. Beim Studium der Vorgänge, welche diesem Zwecke dienen, muss man geradezu staunen, wie exakt die Regulationen arbeiten, die bei einer Verminderung oder Steigerung der Zufuhr in Kraft treten. In normalem—und meistens auch in pathologischem—Zustande verlässt das Kochsalz den Organismus der Hauptsache nach auf dem Wege der *Nieren*. Die Abgabe des Kochsalzes von seiten des Darms ist, wenn nicht gerade Diarrhöen bestehen, eine ausserordentlich geringe. Das vom Magen sezernierte Chlor wird, wenn nicht Erbrechen stattfindet, im Darm resorbiert. Auf dem Wege des Schweisses kommen nur bei stärkerem Schwitzen beachtenswerte Verluste zustande. Allerdings kann hierbei der Kochsalzgehalt des Schweisses nach Untersuchungen von Cramer, E. Harnack, H. Strauss, Brieger und Disselhorst unter Umständen mehrere Gramm pro die betragen. Ein gewisser Kochsalzverlust ist auch auf dem Wege einer reichlichen Tränensekretion möglich. Diese Faktoren spielen aber unter gewöhnlichen Verhältnissen eine so geringfügige Rolle, dass man in allen Fragen des Kochsalzstoffwechsels in erster Linie sein Augenmerk auf die Nieren richten muss. Es ist ausserordentlich interessant zu sehen, wie stark die Kochsalzausfuhr durch den Urin reduziert wird, sobald eine Verminderung der Kochsalzzufuhr stattfindet. Im Hunger wird die Kochsalzausscheidung schon sehr bald auf nur ein Gramm pro die herabgesetzt.

So schied beispielsweise der Hungerkünstler Succi am 11. bis 12. Hungertage nur 0.36 g Kochsalz pro die aus. Ich habe wiederholt bei Magenkranken, welche an abundantem Erbrechen litten, tagelang nur minimale Spuren von Kochsalz im Urin feststellen können. Dass der Mensch bei einem solchen Sparsystem mit recht geringfügigen Mengen von Kochsalz auszukommen vermag, wissen wir schon lange durch Erfahrungen bei nomadisierenden Völkern, welchen nur Spuren von Kochsalz für ihre Ernährung zur Verfügung stehen, aber auch durch exakte Versuche an Gesunden und Kranken. Als solche möchte ich hier die Versuche von A. Mayer, von Ambard u. a. nennen, welche mehrere Wochen hindurch eine Kochsalzzufuhr von nur 1½ bezw. 1¾ g pro die ohne Schaden vertrugen. Was unsere Erfahrungen an Kranken betrifft, so bestätigen die von den verschiedensten Seiten über Chlorentziehungskuren gemachten Beobachtungen die Auffassung vollauf, dass wir den Menschen mit nur wenigen Gramm Kochsalz pro die ausreichend ernähren können. Bunge hat schon vor Jahren 2 gr ganz allgemein als genügend bezeichnet und es erscheint vielleicht zweckmässig, diese Menge als "Nährsalzration" zu bezeichnen, während wir das Plus, das von der Mehrzahl der Kulturmenschen genommen wird, mit dem Namen der "Würzsalzration" belegen wollen.

Auch bei völliger Gesundheit ist der Kochsalzgehalt des Organismus gewissen, allerdings nicht zu grossen, Schwankungen unterworfen. So kann man, wie ich selbst das mehrfach bei Karellkuren beobachtet habe, die an Fettleibigen angestellt wurden, 8 bis 10 gelegentlich auch 12 g Kochsalz dem Körper entziehen. Ambard hat nach einer längerdauernden chlorarmen Ernährung bei sich einen Chlorverlust von 15 g Kochsalz feststellen können. Wird ein Kochsalzvacuum künstlich geschaffen, so zeigt der Organismus das Bestreben, neu zugeführtes Kochsalz solange zurückzuhalten, bis das vorhandene Defizit ausgeglichen ist. Während unter normalen Verhältnissen Kochsalzgleichgewicht meistens schon nach 1 bis 2 Tagen zu erzielen ist, dauert es bei einer starken Verminderung der Zufuhr oder bei einer erheblichen Steigerung der Einfuhr nach vorausgegangener Kochsalzunterernährung meist eine Reihe von Tagen, bis sich wieder die Werte für Ein- und Ausfuhr vollkommen entsprechen. Von besonderem Interesse ist dabei die nicht nur bei Kranken sondern auch beim Gesunden zu machende Beobachtung, dass mit der Kochsalzretention meist auch eine Wasserzurückhaltung einhergeht, und dass mit der Entsalzung des Organismus auch eine Entwässerung des Organismus erfolgt. Die entsprechenden Werte betragen für 10 bis 15 gr Kochsalz etwa 1½ bis 2 kg Wasser. Dies kommt daher, dass die Hauptmasse des Kochsalzes in Form einer "Seroretention" und nur ein geringer Teil in Form einer "Historetention" zurückgehalten wird, wie ich sei-

nerzeit diese Vorgänge genannt habe. Ueber die Grösse der Historetention, die von französischen Autoren "trockene Chlorretention" genannt wird, möchte ich jedoch zurzeit ein bestimmtes Urteil nicht abgeben, da der Vorgang als solcher bis jetzt nur aus Stoffwechseluntersuchungen erschlossen ist. Die zurzeit vorliegenden Kochsalzbestimmungen an den Organen—wie sie von Dunnstedt und Rumpf, Loeper, H. Strauss und Chajes u. a. geliefert worden sind—sind nicht sehr geeignet, für eine grosse Bedeutung der Historetention zu sprechen. Freilich fehlen noch Untersuchungen der Haut bei Retentionsprozessen, die mir wichtig erscheinen, weil Padtberg gezeigt hat, dass schon unter normalen Verhältnissen grössere Mengen von Kochsalz in der Haut Unterkunft finden. Ich habe zurzeit Untersuchungen nach dieser Richtung hin veranlasst.

Wenn der Kochsalzgehalt der Nahrung hochgradig herabgesetzt ist, so macht sich dies zunächst durch eine Herabsetzung des Kochsalzgehaltes des Urins und bei höheren Graden bezw. bei längerer Dauer unter Umständen auch durch eine Verminderung bezw. ein Sistieren der Salzsäuresekretion des Magens bemerkbar. Schon Forster, dessen umfassende Versuche über die Bedeutung der Salze für die Ernährung ja bekannt sind, hat auf diese Dinge hingewiesen und Cahn hat interessante Versuche mitgeteilt, in welchen es ihm gelungen ist, bei Hunden die Salzsäuresekretion durch Fütterung mit chlorfreier Nahrung zum Versiegen und später wieder durch Zufuhr von chlorhaltiger Nahrung zum Erscheinen zu bringen. In Anlehnung an diese Experimentalbefunde haben Osler u. a. den Vorschlag gemacht, bei schweren Fällen von sekretorischer Insuffizienz des Magens, Kochsalz reichlich zuzuführen, und bei Fällen von Superacidität und Supersekretion den Kochsalzgehalt der Nahrung einzuschränken (Romckes, Enriquez und Ambard, Richartz u. a.). Nach meinen eigenen Erfahrungen ist aber mit einem solchen Vorgehen in der Mehrzahl der Fälle nur wenig zu erreichen. Denn es ist beim Menschen der Salzsäuregehalt und die Menge des Sekrets meist mehr von Alterationen der Tätigkeit der sezernierenden Zelle als von dem Kochsalzgehalt des Organismus abhängig. Wenigstens ist es mir fast nie gelungen, bei Zuständen von Anacidität durch reichliche Kochsalzzufuhr die Sekretion wieder in Gang zu bringen, und durch eine Herabsetzung der Kochsalzzufuhr einen einwandfreien Einfluss auf Zustände von Supersekretion zu gewinnen. Dagegen habe ich eine Reihe von Fällen in der Erinnerung, bei welchen lange Zeit grössere Mengen von stark salzsäurehaltigem Magensaft erbrochen wurden, trotzdem der Urin schon wochenlang als Zeichen der Chlorverarmung des Organismus nur Spuren von Kochsalz enthielt. Eine sehr weitgehende Chlorverarmung des Organismus scheint übrigens, wie Wyss betont, auch zu allgemeinen Störungen führen zu können, und ich selbst habe einige Male im Anschluss an maximale Chlor-

verarmung des Organismus—es handelte sich um Fälle von motorischer Insuffizienz des Magens mit abundantem Erbrechen von Magensaft, Krankheitsbilder beobachtet, die unter dem Bilde schwerster Prostration und Spasmophilie einhergingen und nach subkutaner oder rektaler Zufuhr grösserer Mengen von physiologischer Kochsalzlösung verschwanden. Derartige Beobachtungen besitzen ein gewisses Interesse im Hinblick auf die schweren Gesundheitsschädigungen, über welche uns die Kinderärzte nach reichlicher—insbesondere subcutaner—Kochsalzzufuhr berichten. Ich habe hier vor allem das "Salzfieber" im Auge, für dessen Entstehung allerdings mehr das Na-Ion als das Cl-Ion in Frage zu kommen scheint (L. F. Meyer). Unter Berücksichtigung der Untersuchungen von Jacques Löb verdient es besondere Beachtung, dass das Salzfieber oft ausbleibt, wenn man kleine Mengen von K-Ionen und Ca-Ionen gleichzeitig zuführt. Freilich ist zu berücksichtigen, dass der kindliche Organismus auf Veränderungen der Ernährung viel leichter mit Störungen reagiert, als der Körper des Erwachsenen.

Wichtiger als die Kochsalzverluste sind für den Erwachsenen—wenigstens für gewisse Fälle—Kochsalzretentionen. Es ist schon erwähnt worden, in wie hohem Grade die Nieren die Kochsalzausscheidung dem jeweiligen Kochsalzbestande des Organismus anpassen. Welche besondere Bedeutung eine Insuffizienz der Nieren für die Kochsalzausscheidung gewinnen kann, haben wir erst durch neuere Forschungen erfahren. Es ist jetzt fast 10 Jahre her, dass ich auf Grund einer längeren Reihe von Untersuchungen die Auffassung geäussert habe, dass der bei parenchymatösen Nephritikern auftretende Hydrops—im Gegensatz zur kardiogenen Wassersucht—meist durch eine primäre nephrogene Kochsalzretention zustande kommt. Auf Grund dieser Feststellung habe ich damals eine Einschränkung der Kochsalzzufuhr für die Bekämpfung der *Hydrops renalis* gefordert, weil ich zu der Auffassung gelangt war, dass das retinierte Kochsalz zum grössten Teil in Form einer Seroretention im Organismus untergebracht wird, was nur durch eine gleichzeitige entsprechende Zurückhaltung von Wasser möglich ist. Ohne das komplizierte Problem der Hydropsieentstehung mit einer solchen Auffassung als gelöst ansehen zu wollen, glaubte ich doch mit der Entziehung des Kochsalzes ein wichtiges Glied aus der Kette der zur Hydropsie führenden Faktoren ins Auge gefasst zu haben, dessen Entfernung aus der Reihe der anderen Faktoren geeignet ist, die Kette als Ganzes zu sprengen. Meine damals aufgestellten therapeutischen Forderungen wurden alsbald durch die aus Frankreich kommenden Mitteilungen verschiedener Forscher, so vor allem von Widal und Javal, gestützt, welche im Verfolg ihrer Untersuchungen auf anderen Wegen zu denselben Forderungen an die Therapie wie ich gelangt waren. Die Chlorentziehung ist

allerdings nicht als Heilmittel gegen Nierenkrankheiten, sondern nur als Entwässerungsmittel bei vorhandenen oder drohenden Hydropsieen der parenchymatösen Nephritis empfohlen worden, was ich gegenüber einer jetzt nicht ganz selten zu beobachtenden, unexakten Indikationsstellung von Chlorentziehungskuren auch hier scharf betonen möchte. Auch will ich hier die Bemerkung nicht unterdrücken, dass ich für die Behandlung des Hydrops bei Herzkranken, sowie der meist auf cardialer Grundlage entstandenen Hydropsieen bei den Fällen von chronisch interstitieller Nephritis, eine stärkere Einschränkung des Kochsalzes nur für die Stadien hochgradigster Kompensationsstörung empfohlen habe, sonst aber nur eine massvolle Einschränkung der Kochsalzzufuhr das Wort geredet habe, weil nach meinen Erfahrungen bei mittleren Fällen von cardialer Kompensationsstörung die Fähigkeit der Nieren zur Kochsalzausscheidung nur wenig gestört ist. Eine Einschränkung des Kochsalzes in der Nahrung dürfte in den Fällen der genannten Art vorzugsweise durch eine Verminderung des Durstes, sowie dadurch wirken, dass die Nieren bei intakter Ausscheidungsfähigkeit für Kochsalz nach einer Einschränkung der Kochsalzzufuhr, noch eine Zeitlang mehr Kochsalz ausscheiden, als der Aufnahme entspricht. Hierdurch kann, wie bereits erwähnt ist, mit dem Kochsalz auch gleichzeitig Wasser eliminiert werden. Mehr kann ich auch nicht bezüglich der entwässernden Wirkung einer Chlorentziehung bei serösen Ergüssen infolge von Lebercirrhose oder infolge von entzündlichen Prozessen in der Bauch- oder Brusthöhle zugeben. Hierüber sind ausserordentlich verschiedenartig lautende Mitteilungen gemacht worden. Nach meinen eigenen Erfahrungen ist die Wirkung einer Chlorentziehung bei den vorliegenden Krankheitszuständen jedenfalls ausserordentlich inkonstant.

Auch bezüglich Beeinflussung urämischer Zustände, die von einigen Seiten gleichfalls mit Chlorretention in Zusammenhang gebracht werden können, kann ich einem Optimismus nicht huldigen. Ich kann mich sogar des Eindrucks nicht erwehren, dass der anhydropische Nephritiker mehr zur Urämie neigt, wie der hydropische. Die Wasserzurückhaltung scheint hier verdünnend auf stickstoffhaltige Retenta zu wirken, deren Vermehrung, wie ich schon vor einem Jahrzehnt in einer ausführlichen Monographie gezeigt habe, den Boden für die Urämie vorzubereiten vermag. Es ist verlockend, diese Frage weiter zu verfolgen und für die Therapie der Urämie hieraus die entsprechenden Consequenzen zu ziehen.

Für die Therapie des Diabetes insipidus hat dagegen das genauere Studium des Chlor- und Wasserstoffwechsels wertvolle Früchte gezeigt, indem die Aufmerksamkeit für die Behandlung dieser Krankheit nicht bloss auf die Wasserzufuhr, sondern gleichzeitig auch auf die Koshsalzzufuhr gerichtet wurde. Wenn auch nicht für alle

Fälle von Diabetes insipidus, so haben wir doch für eine nicht geringe Zahl von Fällen dieser quälenden Krankheit in der Einschränkung der Kochsalzzufuhr ein wichtiges Mittel zur Bekämpfung der Polyurie kennen gelernt. Auch für zahlreiche Fälle von reiner Polydipsie d. h. für solche Fälle, welche die Fähigkeit besitzen einen Urin mit einer relativ normalen Höhe der prozentualen Kochsalzkonzentration auszuscheiden, hat sich eine Einschränkung der Kochsalzzufuhr durch Verminderung des Durstes als therapeutisch wirksam erwiesen.

Von einer gewissen Bedeutung ist die Erforschung des eigenartigen Verhaltens des Kochsalzes im Mineralstoffwechsel noch für eine bestimmte Frage der Pharmacotherapie geworden. Es haben Toulouse und Richet, Laudenheimer, Bilint u. a. gezeigt, dass der Organismus Brom viel leichter festhält, wenn die Nahrung gleichzeitig chlorarm gestaltet wird, und Böniger konnte im Tierexperiment im Blutserum einen Teil des Kochsalzes durch Bromnatrium ersetzen. Wyss empfahl die Wechselbeziehungen der beiden Substanzen zur Behandlung der Bromvergiftung in Form der Darreichung von grossen Kochsalzdosen dienstbar zu machen. Auch wies Leva neuerdings in von mir veranlassten Tierversuchen nach, dass bei nephrogener Hydropsie-Tendenz Brom weniger leicht Ergüsse erzeugt, als dies beim Chlor der Fall ist, sodass es bis zu einem gewissen Grade als Würzsalz benutzt werden kann. Wenn zwei Salze, die sich chemisch so nahe stehen, wie Chlornatrium und Bromnatrium, sich so verschieden verhalten, so ist es nicht wunderbar, wenn andere Salze ihren eigenen, von demjenigen des Kochsalzes abweichenden Weg gehen, wie ich dies u. a. bei meinen hier schon erwähnten Untersuchungen über den Kochsalzstoffwechsel bei Nierenkranken bezüglich der phosphorsauren und schwefelsauren Salze feststellen konnte.

Nicht so ergebnisreich wie die bisher erörterten Forschungen sind dagegen die Studien auf einem Gebiete gewesen, auf welchem Fragen des Kochsalz und Wasserstoffwechsels schon seit langem mit Eifer erforscht worden sind, nämlich auf dem Gebiete des Fiebers. Trotz zahlreicher alter Untersuchungen, ich nenne nur diejenigen von v. Leyden, Redtenbacher u. a. sowie auch zahlreicher neuerer Forschungen, so z. B. von Schwenkenbecher u. a. sind hier die einzelnen Fragen noch nicht nach jeder Richtung hin völlig geklärt. Wasser- und Kochsalzretentionen scheinen hier jedenfalls nicht konstant zu sein.

Trotz meiner hier in zielbewusster Absicht gewählten Beschränkung auf die Erörterung weniger Fragen—ich wollte auf die Bedeutung des Kochsalzes und des Wassers für den Aufbau und das Wachstum der Gewebe, für den Ablauf von Fermentwirkungen und für die Vorgänge der Entgiftung im menschlichen Körper nicht genauer eingehen—dürfte meine skizzenhafte und wie bereits

erwänt ist, in erster Linie die Pathologie ins Auge fassende Besprechung doch schon einen Begriff von der grossen Bedeutung des Kochsalz- und Wasserstoffwechsels für die Lebensvorgänge gegeben haben. Die Wichtigkeit des Wassers für die hier interessierenden Fragen, hat ihren Ausdruck schon lange in dem alten Salze gefunden: "Corpora non agunt nisi fluida," und es ist dieser von der Chemie stammende Satz mit Recht auch auf den menschlichen Stoffwechsel übertragen worden, da der Körper des Erwachsenen nach Bischoff, Volkmann, C. Voit u. a. etwa 58 bis 55 Prozent Wasser enthält. Der kindliche Körper ist bekanntlich noch wasserreicher als derjenige des Erwachsenen. Von den verschiedenen Ernährungsarten wissen wir, dass kohlehydratreiche Nahrung in besonderem Grade zur Wasserretention disponiert, was nicht bloss durch das Experiment (Bisch, Rubner und v. Hösslin), sondern auch durch die Erfahrungen der Kinderärzte (Weigert, Steinitz u. a.) festgestellt ist, und es spielt möglicherweise dieses Moment auch bei dem Gewichtsverlust von Fettleibigen, wenn diese zu einer kohlehydratarmen Entfettungsdiät übergehen und bei den Haferödemen von vorher kohlehydratfrei oder kohlehydratarm ernährten Diabetikern neben anderen Momenten eine mehr oder minder bedeutsame Rolle.

Dass eine Erhöhung der Flüssigkeitszufuhr die Ausschwemmung von stickstoffhaltigen Schlacken steigert, ist auch durch experimentelle Untersuchungen festgestellt. Dass sie aber, wie man früher annahm, zu einer Erhöhung des Stickstoffwechsels führt, hat sich nicht erweisen lassen. Heilner fand beim hungernden Tier allerdings eine Erhöhung der Kohlensäureausscheidung nach Zufuhr grösserer Flüssigkeitsmengen.

Durch Entziehung von Flüssigkeit erfolgt ein Gewichtsverlust. So hat man bei Hunden (Straub) einen Verlust von etwa 10 Prozent und bei Tauben (Nothwang) einen Verlust von etwa 22 Prozent des Körpergewichts eintreten sehen. Es erfolgt dabei eine Eindickung des Blutes, die 10 bis 20 Prozent betragen kann. Von der Flüssigkeitseinschränkung hat man früher angenommen, dass sie den Stoffwechsel steigert und hat sie deshalb für Entfettungszwecke empfohlen. Es hat sich aber gezeigt (Straub, Dennig, Czerny, H. Salomon u. a.) dass sie nur den Eiweisszerfall steigert, aber nicht die Fettverbrennung erhöht. Ein Stickstoffverlust scheint übrigens auch im Chlorhunger nach den Untersuchungen von Belli möglich zu sein. Eine Flüssigkeitsentziehung findet bald ihre Grenzen. So trat in den Versuchen Nothwang's welche an Tauben angestellt waren, der Tod nach Einbusse von 22 Prozent des Körpergewichts ein, und nach einem Verlust von 10 Prozent waren schon schwere Krankheitserscheinungen vorhanden. Durstende Mäuse starben zehnmal schneller, als hungernde (Landauer). Auch der Mensch

erliegt dem Durst rascher, als dem Hunger, und es haben die bekannten Hungerkünstler (Breithaupt, Succi, und Catti) ihre Rekords wohl in Bezug auf den Hunger nicht aber auf das Dursten geleistet.

Bei einer Betrachtung der Errungenschaften der neueren Forschungen auf dem Gebiete des Kochsalz- und Wasserstoffwechsels ergiebt sich die vom Standpunkt der praktischen Ernährungslehre erfreuliche Tatsache, dass nicht bloss unser Kennen, sondern auch unser Können in den letzten Jahrzehnten Fortschritte gemacht hat. Die Fortschritte unseres Könnens sind dabei mehr der Krankenernährung als der Ernährung der Gesunden zugute gekommen. Für die Ernährung von Kranken hat sich die ärztliche Regelung der Kochsalz- und Wasserzufuhr für eine ganze Reihe von Fällen als ebenso wichtig erwiesen, wie es die Diätverordnungen unter calorischen Gesichtspunkten sind. Die Forschungen eines Liebig, Bennecke, Moleschott, Voit, Rubner, Forster, Hamburger u. a. und hier in Amerika von Jacques Löb, Chittenden u. a. haben aber auch für den Gesunden gezeigt, wie gross die Bedeutung einer ausreichenden Zufuhr von Salzen für den normalen Ablauf der Lebensvorgänge ist. Soweit das Kochsalz in Frage kommt, so liegt allerdings seltener Grund zu einer Vermehrung als zu einer Verminderung der Kochsalzzufuhr vor und es ist die Berechtigung des Bunge'schen Satzes, dass die meisten Menschen zu viel Salz zu sich nehmen zum Mindesten unter dem Gesichtspunkte zu erkennen, das der durch reichliche Salzzufuhr gesteigerte Durst zahlreiche Menschen zu einer Wahl von Getränken verleitet, die ihrer Gesundheit nicht immer förderlich sind. In diesem speziellen Punkte stimmen wir auch mit den Forderungen mancher moderner Ernährungsreformer überein, welche für die Gesunden ganz allgemein eine starke Reduktion des Salzes in der Nahrung verlangen, während wir nicht zugeben können, dass eine solche Forderung sonst nach allen Richtungen hin wissenschaftlich ausreichend begründet ist. Freilich ist gar mancher Punkt auch auf dem Gebiete der Kochsalzfrage noch dunkel. Immerhin ist aber doch unter den Salzfragen das Verhalten des Kochsalzstoffwechsels besonders gut studiert, so dass wir nur wünschen können, dass die künftige Forschung auch für die Verwendung anderer Salze ähnlich scharfe Gesichtspunkte schaffen möge, wie wir sie für die Zumessung des Kochsalzes bereits kennen gelernt haben. Haben wir auch allen Grund, das was wir schon heute über die Bedeutung anderer Salze für den Stoffwechsel wissen, hoch auzuerkennen, so liegt gerade auf diesem Gebiete des Stoffwechsels noch ein grosses Feld brach, dessen Bebauung nicht bloss für die Ernährung des Gesunden, sondern vor allem auch für die Ernährung von Kranken wertvolle Früchte zu bringen verheisst.

DIET AS A WEIGHTY FACTOR OF CAUSAL THERAPEUTICS IN SEVERE DISEASES OF THE STOMACH AND INTESTINES, IN TROUBLES OF METABOLISM, KIDNEY TROUBLES, DISORDERS OF THE CIRCULATION, IN PULMONARY DISEASES, AND IN NERVOUS AND MENTAL DISEASES.

By Dr. W. Plönies, Hanover, Germany.

The great importance of diet in connection with the manifold ailments of the body is due to the fact that, given a correctly regulated diet, the latter in itself is able to correct, in a certain and lasting fashion, the disorders of the gastro-intestinal chemical processes, the processes of fermentation and decomposition of the food. Seeing that the toxins and decomposition products of these processes, being absorbed by the blood, are carried to every organ of the body, they must of necessity tend to produce changes in these organs in a pathological-chemical sense, and at the least through chemical action exert a more or less disturbing influence on the functions of the organs, especially if the latter are lacking in resistance power owing to hereditary or other influence, even if they do not give rise to pathological-anatomical changes in the organs. Again, in disorders of the stomach a further factor may lead to more or less pronounced disturbances in different organs, inasmuch as lesions of the mucous membrane, particularly the mucous membrane of the stomach, which are very frequently present at the same time, often enough latent, may induce irritation along the ramifications of the N. vagus and N. sympathicus. This may occur as the result of partaking of improper foods or beverages, or may result from other causes, which have been fully dealt with in another work.[1] Inasmuch as in such complications a correct diet lessens the irritation caused by the stomach lesions, and, in conjunction with the absolutely indispensable bodily and mental rest, it may result in a healing of the lesions themselves, a dietary treatment is of itself able to bring about an immediate and lasting dispersion of the extremely numerous irritation symptoms which are observed in the brain, and also in the mind, in the cranial nerves, the organs of sense, the throat, the heart, the lungs, the back, and even the extremities. These are cases in which, up to the present, medicines could have, at the most, only a transitory effect, or fail altogether, for here medicines alone could not possibly benefit, owing to the continued existence of the predisposing cause, and to the impossibility of removing the latter by medicines alone. These are disorders, which, having been regarded as of nervous origin, have hitherto occupied the attention of specialists for nerve diseases, and which even to a certain extent assert their place in the text-books as independent diseases, although they are in fact nothing more than symptoms of a disease. For dietary treatment there will thus come in question such disorders of

the body as are brought about by chemical toxic influences, or by irritations propagated along the nerve tracks. For the ordering of the diet with regard to the processes of fermentation and decomposition, we must ask ourselves which sections of the digestive tract are to be taken into chief consideration. It has been shown elsewhere [2] that only the stomach and small intestine need to be considered, as the processes of decomposition in the large intestine, in which the colon bacteria play a part, are, as is well known, of a physiological nature, their principal function being probably to render accessible to the process of resorption the nutritive salts included in the cellulose. In this connection my own views diverge decidedly from those of Metschnikow, who regards the decomposition of the contents of the large intestine as giving rise to toxical action. His therapeutic efforts to combat decomposition in the large intestine by introducing other bacteria, belong to the category of endeavors which seek to change the laws of nature, and to improve upon the entirely wise rules which she has laid down. To be logical, and to conform to natural laws, the diet, in order to prevent fermentation and decomposition in the stomach and small intestine, must, for the reasons stated, be so arranged that what is eaten or drunk can not possibly ferment or decompose in those organs; furthermore, such food must be so finely divided, or allow of such fine division by the act of mastication, and at the same time be so rightly warmed, that, when stomach lesions are present, irritations of the latter, in the so frequent complications with ulcers of the large intestine and with appendix trouble, may be avoided. When compiling the diet in connection with the treatment of gastrointestinal disorders, particularly of stomach lesions, there has hitherto been too little attention, or none at all, paid to the exceedingly significant pathological-chemical derangements of the stomach. There has been at the most a careful observation of the variations, often so capricious, in the hydrochloric-acid contents of the gastric juice, which, however, as has been shown elsewhere,[3] are entirely valueless, both in their bearing on the nature of the diet and on the treatment itself, whilst for purposes of diagnosis the indications thus yielded can be utilised only with the utmost precaution, and stand in striking disproportion to the amount of incommodation, to which the patient is subjected in determining them, and to the risks of injury to the mucous membrane, of hemorrhage, etc., which are involved. It is to the circumstance, that the processes of fermentation and decomposition in the stomach have hitherto not received proper consideration, and to this alone, that I ascribe the fact that, in consequence of the faulty direction of our therapeutical as also diagnostical efforts, the extraordinarily severe and varied afterconditions of these pathological-chemical gastrointestinal disorders were not hitherto recog-

nized in their primary connection, but were invariably regarded either as independent, accidental complications, or were, particularly in the case of latent diseases of the stomach, looked upon as the principal or sole disease, the disease of the stomach being entirely overlooked. In the failure to recognize the causal connection one has even gone so far as to regard the gastrointestinal symptoms, which present themselves, as the effect of an aftercondition, nervousness, which is almost always present, being, as it is, the earliest and most readily occurring feature; this in its turn has led to the supposition of a nervous dyspepsia, which, however, I have never met with, and the existence of which I must dispute, as did my one-time chief, Kussmaul. For if both the pathological-chemical disturbances of the stomach, and also its lesions, are fully taken into account in arranging the diet, one sees clearly, in every single case of illness, where the regulations as to diet and rest are scrupulously observed, how all the complications and symptoms in other organs arising from these disturbances, and finally the nervousness itself, spontaneously and without the administration of medicines, gradually disappear. One can observe how vast and absolutely reliable is the influence of correct diet in removing disorders, often so grave as to endanger life, so long as there are no pronounced pathological-anatomical changes in the organs themselves. Against these changes in other organs diet is, of course, powerless. Here perhaps medicines, so far as is possible for them, or surgical interference, if this is indicated at all, may influence therapeutics.

Among the articles of food which ferment and decompose, and thus not only hinder the removal of fermentations and decompositions, but also maintain these processes in the stomach and small intestine, mention is to be made in the first place of sugar—saccharose as well as levulose and lactose, although the latter is least injurious in the effects of its fermentation. From this it follows that all articles of food and table luxuries and also all tonics which contain these forms of sugar are excluded from this diet. Particularly in the case of tonics I have so often noticed to my great regret that tonics, excellent as regards their other constituents, are rendered, through the sugar which is added to improve the flavor or on account of its being readily assimilable, entirely unsuited for use in all debilities and disorders of the body or nervous system arising from gastrointestinal complaints. The attention of manufacturers and inventors of such tonics is to be particularly directed to this faulty state of affairs. For this reason also fruit is rigidly excluded, although recommended as so beneficial, as well for stomach complaints and the severe intestinal disturbances and diseases which, as shown elsewhere,[4] almost always accompany these complaints, as also for the

disorders of metabolism arising from stomach or intestinal ailments. The fruit recommended for constipation, and in a more marked degree the vegetarian diet recommended by quacks and followers of the so-called "natural" methods of cure, not only aggravate the primary stomach complaint, but have also a gravely prejudicial effect on the lesions of the large intestine usually present at the same time. Multiplying the fermentations and decompositions, they intensify the atony of the intestine, which is brought about by the toxins of these processes, and have frequently enough a pernicious influence on a latent appendicitis contemporaneously present, on lesions of the large intestine, but above all on the gravely disordered functions of the small intestine. From observations extending over nearly 30 years, I am convinced that in connection with diet no such rank offences are committed as in the dietary treatment of intestinal disorders, directly the primary chemical disorders of the stomach are overlooked, and so find no consideration in the scheme of diet. The significance of this faulty vegetarian diet for the causal treatment of the functional disorders of the small intestine and of the pathological-anatomical changes in the large intestine, is seen in the fact that, in my personal experience, since I have carefully followed the causal connection of injuries of the functions of the small intestine, of ulcerous disorders of the large intestine, and of appendicitis with stomach complaints, I have never observed a single case of small-intestine disorders, of appendicitis, and of ulcerous disorders of the large intestine only two cases, in which a primary stomach ailment was not demonstrable. I can therefore only warn most emphatically against such vegetarian "cures," on account of their association with such grave danger for the primary disease, for the secondary intestinal injuries and ailments, and indeed for the entire body, apart from the fact that such dietary treatment, for which our intestinal canal is entirely unadapted, offends against the laws of nature, against the structure of the intestinal tract. But nothing avenges itself quicker and more certainly than do offences against nature's laws!

As a further important requisite in the diet to be compiled for gastrointestinal ailments and their after-conditions comes the total exclusion of fat and butter, and therefore of all articles of food of which butter and fat form a part. This necessity, too, has hitherto not been taken into consideration. I need here only allude to the milk so frequently lauded as dietary remedy in stomach complaints. In general, as is well known, fats are the more difficult of digestion, and the stomach, disturbed in its chemism, shows itself the more outraged, the higher the melting point of the fat lies. Of fats, the most easily digested is butter, and the latter is therefore tolerated by the stomach, in the convalescent stage, before all other fats. As butter

must often be used in the cooking of meat, the latter when ready should be freed from the butter by rinsing in hot salt water. As milk and the yolk of eggs both contain fats, their exclusion in all cases of fermentation and decomposition in the intestinal tract is imperative. In the case of milk there comes in question, as a further injurious constituent, milk sugar. Even the nutritive salts of milk may operate in a manner favorable to the conditions of the life of the bacteria. For these reasons milk, which is so largely praised as a remedial article of food, can henceforth have no place in our dietary scheme, apart from the fact that milk, when taken in an uncombined condition, that is to say, not cooked together with flour, rice, groats, cocoa, etc., clots in the stomach to form lumps of curd, which, in the presence of gastric lesions, positively irritate the latter, or at the least decidedly hinder their healing. This is manifested clearly enough by the feeling of oppression and fullness in the stomach and, in the case of advanced lesions, by the gastralgia which set in, a fact which has hitherto been overlooked by almost all specialists for gastric diseases. Yolk of egg is also to be forbidden in contemporaneous disorders of the large intestine and appendix, but above all and always in diarrhea, throughout its whole duration. The fat of meat broth is best removed by means of a funnel; owing to the readiness with which decomposition takes place, or in other words, bacteria develop, it is not advisable to allow the broth to cool in order that the fat may be skimmed off. As the decomposition products of fats and butter have an astoundingly more toxical action, as the results of investigations show, than the fermentation products of the various sorts of sugar, the most rigid exclusion of these is called for.

At the same time a diet, or article of food, absolutely free from fat in a chemical sense is not essential to the carrying out of such a dietetic treatment, no further stipulation being necessary than that fats and butter shall be kept down to the lowest culinary minimum possible. In the preparation of the food, all seasoning is to be avoided; salt alone is permissible, and even this must not be present in excess, out of considerations of thirst and to prevent irritation of the mucous membrane. Particularly when inflammation or irritation of the kidneys is present, the use of salt should, as is well known, be restricted as far as possible. As starch, white of egg, and lean meat do not tend to produce fermentation and decomposition in the intestinal tract, these substances in their different forms must serve for the nourishment of such invalids. Starch will be given best in the form of slices of dry toast or rolls three days old, both of which forms of bread are very readily broken up by the act of mastication, or in the form of roasted wheaten flour, and in various other forms, such as Knorr's barley meal and oatmeal, Hohenlohe's rolled oats passed

through a hair sieve, potato-sago, groats, rice soaked for twelve hours, flaked rice, barley passed through the hair sieve, all of which will be given in the form of soups or porridge made with water, to which a little salt has been added. Where disorder of the large intestine is a complication, oaten preparations are to be avoided, on account of their tendency to give rise to flatulence. In the place of vegetables are to be recommended the flour of rice, thick groats, flaked rice, flaked barley, vermicelli and mashed potato. It is of the utmost importance to render these soups and dishes more palatable, and above all more nourishing, by cooking them together with casein, with white of hen's egg, Leube-Rosenthal's meat solution, or Liebig's meat peptone. The last two preparations, however, as also meat gravies, stimulate the more copious secretion of the gastric juice; when, therefore, a condition of pronounced irritation of a gastric lesion is present, they are to be excluded from the diet until the irritation symptoms of the gastric lesion have subsided, and the latter has commenced to heal. As an absolute necessity is to be regarded the addition of the aforementioned albumen preparations, whenever certain indications, such as hemorrhages, prohibit other forms of nourishment, or when the presence of kidney inflammation or gout forbids the taking of red meats. Furthermore, in the absence of gastric lesions, macaroni and coarse vermicelli, taken as vegetables, may have a place in the diet.

Other kinds of bread, and particularly the Graham bread recommended for constipation, are to be strictly forbidden, on account of their being too difficult of digestion. Among meats are to be recommended, when lesions are present, as soon as any more pronounced local irritation symptoms have subsided, calf's sweetbread, calf's brains, pigeon, partridge, other young wild fowl, and chicken, all roasted, freed from fat in the manner described, and with the skin removed, and, furthermore, raw ham scraped with an iron spoon and carefully freed from fat, fiber, and sinew. Where stomach lesions are on the point of healing, scraped raw loin of beef, in the form of underdone beefsteak, may be permitted, and where stomach lesions are entirely absent, any tender roast meat, veal excepted, freed from fat and without the gravy, is to be allowed. All these meats, under like conditions, may also be eaten cold. As soon as the fermentation and decomposition processes in the stomach have been removed, for the determination of which the size of the heart is the surest guide (as then in adults the R. D.=0, the L. D.=7—8 centimeters), the diet may be broadened in respect to fats, but only after a week to a fortnight in cases where the fermentation and decomposition processes have not been of very long duration, and after three to five weeks when these processes have persisted some considerable time. The first step in this direction will be the addition of fresh butter

to the diet. Only when this can be safely taken, the surest guide to which is afforded by the cardiac measurements remaining constant, as indicated above, may yolk of egg be given, also eggs boiled for 1½ minutes, always assuming the absence of complications of the large intestine; then, and not till then, is milk permissible, but, for the reasons already given, only in combination with other forms of food. As I have described the diet in fuller detail elsewhere,[5] this short account will here suffice.

What absolutely reliable indications have we at all that the processes of fermentation and decomposition in the stomach and small intestine have subsided, and, what is at least of equal importance, what signs are there of the recurrence of these processes after the widening of the diet—indications which are absolutely indispensable for the carrying out of a treatment which is to proceed along sure lines? Subjective troubles are an entirely unreliable guide; they come generally too late, or may be absent altogether, even though the processes of fermentation and decomposition are at work in the stomach and small intestine. Of these may be mentioned loss of appetite, foul-smelling breath, eructations, heartburn, etc. The indications, which I have found after investigations extending over more than 20 years to be the best and most reliable, are such as invariably occur side by side, are invariably present, and which can always be determined earlier than all others. These are the more reliable, that they render us—and herein consists their chief value—altogether independent of the statements and subjective condition of the patient. They invariably allow conclusions as to the presence and the disappearance of fermentations and decompositions in the stomach and small intestine, because their evidence, as an after-condition based upon natural laws, stands and falls with the presence of these processes. These indications are the stomach height, i. e., the distance of the large curve of the stomach from the lower edge of the sternum in the middle line; secondly, the width of the colon (preferably colon transversum); thirdly, and of chief importance, the width of the heart at its base, to which a brief allusion has already been made. The heart width and stomach height are, except in stenosis pyloris, enteroptosis, in the presence of valvular defects of the heart not compensated by changes in the cardiac muscle, and in approaching cardiac paralysis, invariably the same, directly they exceed the normal dimensions—that is to say, become pathologic—and the colon width marches parallel with them in strict arithmetical ratio, except that in diseases of the large intestine the width of the colon may swerve from the proportion to the extent of an increase of 1 centimeter, when stomach and heart, as result of a correct diet, have again become normal, or disease of the large intestine pro se (independently) exists.

The normal stomach height in adults is 8 centimeters; when the stomach is entirely empty it may be 1 to 1½ centimeters less. For the heart the normal dimension is 8 centimeters or less, as is the case with persons of small build, particularly in the convalescent stage, when the measurements may be 7, or even 6½ to 6 centimeters in the lying position and in the standing position the measurement may be 7 or 8 centimeters. The right diameter must always, even when cardiac defects are present, be reduced to 0. In the latter complication the left diameter may then be as much as 2 centimeters larger, where there are old defects of the aortic valve even 5 centimeters larger, without there being need to assume the presence of gastic fermentations and decompositions, with respect to which the stomach height and the width of the colon must then decide. For the colon transversum the normal measurement is 3½ centimeters in the case of men; in small-built women 3¼ or even 3 centimeters. The parallelism of these dimensions, as soon as they have become pathologic, is so constant that, given the heart width, one can conclude with absolute certainty as to the stomach height and width of colon and vice versa, e. g., the colon width pointing to the width of the heart. The truth of the former statement I have had the pleasure of demonstrating to many of my colleagues, and of the latter, in the case of a patient who was an entire stranger to myself, to Dr. Römer, of Illenau. If during the treatment of a case the pathological measurements of the heart, stomach, and colon do not recede, we have at once an absolutely certain indication that in the ordering of the diet mistakes have been made in respect to the withholding of fats or sugars, or else warmed-up food has been given, which also tends to keep up or aggravate fermentation and decomposition in the gastro-intestinal canal. Should the addition to the diet of butter, egg, and milk (the latter being preferably given first diluted to ascertain to what extent it is tolerated), after the subsidence of the fermentation and decomposition processes, result in pathological measurements of heart, stomach, and large intestine being obtained, we know at once that fermentation and decomposition in the stomach have again to be reckoned with, and that butter, yolk of egg, and milk must be struck out of the diet if we are not to endanger the certain success of our treatment. The decompositions, which are confined to the large intestine, have not this effect on the heart and stomach, but, at the most, only on the colon itself. The cause of these changes in the organs mentioned is to be found in the paralyzing influence of the toxins produced by the pathologically changed digestive processes in the stomach and small intestines.

It is to this guiding fact alone that I owe my certain conclusions, on which are built up the results of my investigations in the central

nervous system, particularly in the field of mental diseases and the disorders of the cerebral functions, but also in the disorders of metabolism, and in diabetes mellitus, conclusions which, however, in themselves enabled me to overthrow the so perverse views concerning diet and several dietetic articles of food, such as milk and fruit, which have obtained up to this day, and to build up a diet which will always hold good so long as the laws of nature remain, on which alone that diet is based. The cognizance of these indicators of fermentation and decomposition relieves us from the necessity of a chemical examination of the contents of the stomach, as the determination of the hydrochloric acid content for its bearing on the nature of the diet is, as already mentioned, entirely unnecessary. On the other hand, to touch here on this point also, I regard the examination of the feces as indispensable, for this yields us most valuable indications concerning the functions of stomach, small and large intestine, but above all, concerning the extent of the injuries of these functions caused by the processes of fermentation and decomposition in the stomach and small intestine, yielding us a complete picture of the disease in its entirety such as the minutest examination of the gastrointestinal canal by the methods of percussion and palpation can not possibly afford. The extent of these injuries gives us interesting information concerning the duration and the intensity of the fermentation processes, the variety of the pathogenic bacteria, and the nature of the fermentations and decompositions. These injuries are, as a rule, most severe in those cases where the latter processes have been at work from earliest childhood and where the artificial feeding resorted to in place of suckling prepared the ground for grave diseases during the whole life. The examination of the feces confirms, furthermore, the results obtained by the percussion test for sensibility in the gastrointestinal canal, as is the case when blood is found in the feces, and give us indications of great value for the diet, allowing us to avoid overtasking those very functions, which show themselves most damaged, and thus to lighten, as far as possible, the work of the diseased digestive tract. In doing this we fulfill the first condition, without which a complete cure of the gastrointestinal canal is inconceivable. How sadly is this method of examination neglected, even by authorities on gastrointestinal diseases, although it is so important that every physician should unconditionally be conversant with it.

The aforementioned three indicators of the fermentation and decomposition processes are much more closely bound up with the setting in, and especially with the disappearance of, these troubles, than all the other toxic manifestations independent of the statements and sensations of the patient of which I have knowledge. This conclusion is grounded on careful observation of a very large number of

cases extending over a period of 25 years. A number of my colleagues, too, who have already adopted or tried my methods of examination and treatment, have indorsed the correctness of these observations, among others Dr. Holtzmann, of Strassburg, and physicians attached to the hospital at Illenau. I will devote only a few words more to the determination of these three indicators.

For measuring the heart-width we have the following aids: Ausculto-percussion and ausculto-phonation (my first methods of examination), Bazzi-Bianchi's phonendoscope, Goldscheider's glass stick, and the determining of the apex impulse of the heart, all of which yield the same result. For determining the stomach-height I have always been guided by the palpation of the stomach-colon boundary, which, after a little practice, by a gliding palpation from above downward, the patient standing, is perceptible with absolute certainty. Furthermore, all the aforementioned methods for the heart give the same result. Percussion with the finger on Goldscheider's glass stick applied slantingly gives a hollow sound by percussing upward at the stomach boundary. I may remark here that the instrument just referred to is extremely easy to manipulate, and one which has become indispensable for me in my examinations. For determining the width of the colon the same methods of examination are applicable. The lower boundary is sharply delineated by Goldscheider's glass stick, percussion from the small intestine upward or sideways giving at once a deeper note, as against the higher note of the small intestine. Here again we find the same results, sharp to a degree, with all the methods of examination. Auscultophonation is an easily learned procedure of my own discovery for determining the extent of organs and of tumors, applicable also in the case of the lungs for ascertaining the extent of centers of thickening, all that is required for putting it into practice being an ear trumpet and an ordinary tuning fork. All these methods are easily learned, can be carried out by every physician, and are in point of trustworthiness, when their results are compared one against the other, far superior to the Roentgen-ray method, which affords no guaranty against falling into the most glaring mistakes, as fresh cases every day clearly prove to me. The Roentgen method is, indeed, more in keeping with the spirit of our day, which would dispense with all practice, all accurate thinking and careful weighing of results, all overexertion, above all, however, all loss of time, e. g., in the establishing of the diagnosis, but in keeping with the proverb, "nil sine magno labore," a well-founded diagnosis, laying clear the causal coherence of the case, will never be established without these pains and sacrifices, and only this sound and well-laid foundation will make it possible for us to build up a successful therapy, which, being causal, is sure and certain within the limits of human power.

In the case of patients with naturally inferior or weakened central nervous system, disturbances such as light and restless sleep, the recurrence of convulsive movements before falling asleep, failure of mental working power, ill-humor, as results of toxic influences arising from the fermentation and decomposition processes, and with other patients now and then local troubles, such as eructations, pyrosis, etc., may announce the reappearance of fermentation and decomposition following on a broadening of the diet, earlier than do the indications already described, afforded by the heart, stomach, and large intestine. Such data, however, always render us dependent on subjective troubles, i. e., such as are grounded on the feelings of the patient, and which may be transitory and have for their moving cause other circumstances, as a state of violent mental excitement, etc., that is to say, are not entirely unquestionable.

It would be a grave sin of omission on my part were I to make no mention of the extreme importance of bodily rest, freedom from excitement, vexation, etc., in a word, mental repose, for the healing of lesions of the whole digestive tract, above all for the healing of stomach lesions, to which I have already referred elsewhere.[6] But there is another reason why rest is in general indispensable, viz, that it enables the digestive processes, particularly in the stomach, to proceed quicker and also more effectively. Not less weighty is the circumstance that rest reduces the caloric requirements of the body to a minimum; hereby again is moderated the loss of calories to which the absolutely essential withdrawal from the diet of fats, and the so readily assimilable sugar, subjects the body, with the result that emaciation is counteracted as far as possible. This contemporaneous rest cure—apart from the complications of hemorrhage, gastralgia, acute appendicitis, etc., which of course demand it—is urgent in proportion to the extent of the stomach lesions, the latent appendicitis, and the lesions of the large intestine, and also in proportion to the degree of the weight shortage present, to the severity of the small intestine injuries, and thus to the difficulty with which the process of anabolism is carried on. But more strictly than ever must we insist upon this rest treatment when we have to do with more extensive latent tuberculous foci in the lungs, threatening pleurisy, which are here so extremely common. By this means we shall attain our end far more quickly and with far greater certainty, and shall have much less to fear from progressive emaciation and loss of strength. If, in the case of patients who refuse to accommodate themselves to the requirements of the rest cure (particularly when severe injuries of the small intestine and more extensive gastro-intestinal lesions are present), we decline from the outset to undertake the treatment, we shall spare ourselves many an undeserved

reproach, as the patient always forgets to ascribe to himself the mischief resulting from his disobedience to his doctor's injunctions. That the drawbacks of a rest cure in which the patient maintains the recumbent posture can be counteracted by passive massage of the extremities needs no arguing. With the same end in view, the prevention of emaciation, such medicines as bismuth carbonate, magnesium peroxide (Merck), should be restricted as far as possible where there is a severely reduced state of nutrition, but especially does this injunction apply to resorcine and benzonaphtol in the case of disease of the large intestine, as the frequent administration of these medicines during the day results in reduction of weight, which can be avoided by the withholding of these remedies.

For which diseases and manifestations of disease does this diet come in question? First and foremost, of course, for the treatment of chronic gastric catarrh, which is very rarely met with unaccompanied by gastric lesions, and which without this complication is almost entirely confined to the male sex. This diet comes, furthermore, in question for the lesions of the stomach, which, according to my experience, extending over more than 25 years, are most frequently latent, i. e., without extensive and visible hemorrhage and unaccompanied by severe pain, and which also generally go along with fermentation and decomposition processes in the stomach and small intestine. Furthermore, this diet is absolutely necessary for the treatment of dilatation of the stomach. So long as there are no extensive cicatricose contractions of the pylorus, which in the manner already suggested are easily diagnosed, the most pronounced dilatation of the stomach will, under this diet, with absolute certainty shortly subside. I regard, therefore, the washing out of the stomach not only as unnecessary, but also as directly hazardous on account of the dangers and disadvantages discussed in the foregoing and elsewhere,[78] the more so that without this diet such washing out can never entirely disperse the fermentations and decompositions, and that this procedure, on account of the weakening of the mucous membrane of the stomach, at least renders it difficult to bring the stomach into a state in which fats and sugar are tolerated. This weakening of the mucous membrane of the stomach results from its lixiviation by the irrigation fluid in spite of the use of physiological salt solution and manifests itself each time in a reduction of the bodily weight of the patient to the extent of, generally, 500 grams. Anyone who weighs all this against the invariably only transitory improvement, which can result from the washing out of the stomach when unaccompanied by a correct diet, will, as a conscientious physician, discontinue this practice and resort to it only in exceptional cases, such as those of threatened poisoning, etc., where it remain an indicatio causalis and operates as a life-saving resource.

Furthermore, our diet comes in question for the healing of the lesions of the duodenum, for the restoring of, or, where this is no longer possible, for the amelioration of the vastly important functions of the small intestine, which after a lengthy duration of the gastric disease are generally severely injured and the injuries of which are solely a result of fermentation and decomposition of the stomach contents, that have been going on for many years. As we know, the small intestine is the most important part of the whole digestive canal; the mere injuring of its bactericidal function, which, as investigations have shown, is so easily destroyed, has a directly pernicious influence on the rest of the body and is the cause of cystic ailments and the formation of gallstones, for I have never seen disease of the gall bladder without accompanying disease of the stomach and small intestine. Careful clinical examination is here more reliable than examinations in the dissecting room.

The destruction of the small intestine's capacity for killing disease germs is the sole cause of appendicitis. Very frequently appendicitis can be observed as latent disease in gastric complaints, and may exist as such for many, many years, until, as the result of encroaching on the peritoneum, it enters upon the acute stage. The destruction of the bactericidal function of the small intestine is the sole cause of ulcerations of the large intestine, which also are very commonly latent. It is, however, also the most common and most important cause of the invasion of tuberculosis in the body and of the invasion of other infectious diseases, such as typhus abdominalis, dysentery, etc. In the immunity against these infectious diseases an unimpaired condition of the bactericidal function of the small intestine probably plays an important part. No small rôle is played also by the injury of the small intestine functions caused by fermentations and decompositions, and not less important is the direct influence of the toxins of these processes on the pancreas in the injuries of the pancreatic functions and the diseases of the pancreas. No other procedure, no other remedy, can, according to my careful investigations, repair, or at least improve, the damaged functions of the small intestine than the putting an end to the fermentations and decompositions in the stomach by means of the diet, and by imposing the lightest possible functional burdens on the small intestine, which, as my experience of many years goes to prove, can only be achieved by the diet under discussion. Even severe injuries of the functions in question, after a six months' carrying out of the dietary treatment, are considerably ameliorated, as the results of the examination of the feces go to prove, and where the fermentations and decompositions have not persisted too long, can be entirely, or almost entirely, cured. A further urgent warning I would direct against the spa treatment, where the waters have a purgative action, and this is particularly directed against the cures

at Karlsbad, Marienbad, and Neuenahr, which, as experience and observations show, only aggravate the condition of the functions of the small intestine, and also of the stomach functions, and which, by heightening the stomach's intolerance, only further accentuate the fermentation and decomposition. The transitory improvement, which takes place at such spas, can be ascribed only to that most weighty factor of bodily (and very often mental) rest, and the relaxation which the cure affords, but which can be obtained in equal measure in sanatoria and at ordinary health resorts. The practice of drinking the waters at spas, and here I make no exceptions, is entirely superfluous, and without this dietetic treatment never accomplishes its end, even when not detrimental in the manner already described. Even in association with this diet it can not, according to my investigations, accelerate the course of healing. The accentuation of the fermentations and decompositions caused by the taking of purging mineral-water cures, or which can even result from partaking of cold mineral waters, is the cause of the severe cardiac disturbances, the severe sleeplessness, severe melancholia, which set in after such cures.

This same diet is called for in ulcerous diseases of the large intestine, in latent typhlitis, and in diarrhea. The latter is not to be cured except by the most rigid observance of diet, and as a rule does not require the administration of opiates. In this intestinal complication I prescribe bismuth. carbonic. 10, bismuth. bisalicylic. 5, catechu pulv. 4, benzonaphtol 2, of which I give as much as will cover the end of the blade of a dinner knife up to half a teaspoonful two hours after meals, in warm weak black tea, which in such cases I give also as a beverage. Constipation is generally only a result of the aforementioned atony of the large intestine, caused by the toxins of the fermentations and decompositions, but which, where ulceration of the mucous membrane of the large intestine is present, may also be due to spastic contraction of the large intestine at the seat of the ulcers, being very seldom conditional alone on hemorrhoids following on stricture of the sphincter. This constipation can be combated only with this diet, if the causal indications are to be satisfied. Where there are strictures of the sphincter, not infrequently associated with particularly severe local atony of the rectum, these must be put an end to by dilating the sphincter. It is not to be denied that this diet has a constipating tendency, and that at first the constipation tends to increase. For all that, the diet must not be changed, as otherwise atony and ulcers of the large intestine—not to speak of severe injuries to the stomach and small intestine—as was shown in an earlier section, can never heal; on the contrary, these conditions could only be made worse, and all for the sake of the temporary success of evacuation achieved. For the same reason all purgatives are strictly forbidden; they would, above all, severely

injure the functions of the small intestine, and would also, as shown elsewhere,[9] have a gravelly injurious effect on the digestion and resorption of the food. As a matter of fact one finds only too frequently the severest injuries of the functions of the small intestine, as observations go to prove, in those cases where a misuse of purgatives, extending over many years, was to be recorded. The constipation must be combated only by the use of glycerin suppositories, injections of camomile tea, oil, or liquid paraffin, until spontaneous evacuation results.

I wish to refer also to the great importance of this diet, here of course only in its liquid form, in cases of typhus abdominalis. For the speedy healing of the lesions of the small intestine, and for the causal combating of cardiac weakness, and the prophylaxis of hypostatic pneumonia, this diet is indispensable, and conduces more quickly and certainly than anything else to the reduction of fever. As all my observations teach me, the continuance of high fever, stupor, and cardiac weakness are due only to a wrong diet, sometimes to the giving of milk and yolk of egg, and when the patient is put on a correct diet, a reduction of the high temperature immediately follows, until by degrees the fever entirely subsides. This same diet is alone competent in the treatment of dysentery. That in the early stages of infectious diseases of the digestive canal antiseptic purgatives are indispensable is too well known to need argument.

Also for disease of the gall bladder and in icterus catarrhalis this diet is alone indicated, taking into account as it does at the same time the indicatio causalis. If the stage of gallstone formation has already been reached the diet can of course do nothing for this complication, although it must be resorted to for the removal of the primary disease, that of the gastrointestinal canal, which must never be neglected. I can not refrain from expressing here my keen regret that surgeons, in consequence of one-sided examination of their patients, are constantly overlooking this primary disease and, indeed, often enough even deny its existence, through ignorance of the proper methods of examination, or, what is still worse, they confuse for the same reason a gastric lesion with cholelithiasis, or with adhesions of the gall bladder, with the result that an entirely mistaken operation is undertaken. If there is a definite diagnosis of cholelithiasis, without immediate surgical interference appearing necessary, I consider it always advisable, before the operation is undertaken, to relieve first the primary disease, as then, thanks to the removal of the cardiac weakness, resultant on the treatment—which weakness almost always goes with the primary disease—the operation is attended with less risk and offers prospects of a more favorable course of healing. The attempt to disperse gallstones by hydro-

therapeutics or medicines is useless. Whilst we must give due recognition to the successes which surgery has achieved in the treatment of cholelithiasis, still the one-sided treatment of what is only a complication, without at the same time removing the primary disease, attended as it is with so many dangers, can never guarantee for the patient an entirely satisfactory result. To touch at this point on the remaining abdominal complications which call for surgical interference, it is to be remarked, that appendicitis, as many observations go to prove, only very seldom requires surgical procedures. The dietetic treatment of the disease of the stomach and small intestine, which is always present, removes also the latent appendicitis quickly and surely. We have success even when the disease is accompanied by severe local pain. In all my 30 years of professional activity I have only in two cases—in which perforation had led to abscess formation—had to call a surgeon to my assistance. In gastric affections, too, unprofitable surgical procedures are far too frequent.

In many cases the gastroenterostomy was undertaken, or suggested, as last resource, after the patient had submitted for a long time to a treatment which could not be successful, because it did not provide for a correct diet and, often enough, for the absolute rest so indispensable. It is overlooked in such cases that a gastroenterostomy has no effect whatever on either the severely injured mucous membrane of the stomach with its lesion, or on its functions. For this reason the gastroenterostomy has never any other influence on the gastric lesion than a rest cure of equal duration and with the same diet would also have. The operation is always without influence on the fermentations and decompositions in the stomach, as underlying the latter is solely the inability of the stomach to tolerate foods capable of giving rise to these processes, and this inability can never be influenced by such an operation. Frequently enough, as has been shown by careful investigations, in the case of such unfortunate patients, with all their troubles associated with the disease of the stomach, small intestine and colon remaining unchanged, another ulcer formation at the place of connection of stomach and small intestine comes to add to their sorrows. Gastroenterostomy is indicated only in cases of more pronounced stenosis of the pylorus, where there is difficulty in emptying the stomach. I have hitherto only once had to recommend such an operation, in a case in which there was at the time no longer any gastric lesion; 10 years later the case presented itself again with a new lesion of the stomach, a lesion of the small intestine near the place of connection, with severe disease of the small intestine and colon following on marked gastric fermentation and decomposition processes, all of which the operation was powerless to prevent, though performed in irreproachable manner by an extraordinarily capable surgeon, Geheimrat, Dr. C.

Before I leave the subject of the diseases of the gastrointestinal canal and its annexions, I wish to refer briefly to a simple method of examination for the diagnosis and the differential diagnosis of lesions of the mucous membrane, particularly as applicable to the determining of the exact location of these lesions, but also the completion of their healing, a method, the application and value of which I have discussed in more detail in another work,[10] viz, the test of the percussory sensitiveness. This method is equally adapted for the determination of gastrointestinal lesions and lesions of the duodenum, as also for the determination of gall-bladder affections, particularly latent affections, and gallstones, also of latent appendicitis, without doing injury to the patient, in contradistinction to the test of the sensitiveness to pressure, which must invariably aggravate the lesions and which, by causing perforation, may even result in a hitherto latent appendicitis becoming acute. For this reason I apply the test of sensitiveness to pressure in the case of the colon, S. Romanum, and the appendix, only after the percussory test of sensitiveness has shown itself to be negative of result, even with the most forcible percussion, and when I wish to convince myself at any cost of the intactness of the intestinal sections in question. This test of the percussory sensitiveness will be best carried out on the organs of the abdomen with the patient in an erect posture. Of the greatest importance is this test of sensitiveness also in pulmonary tuberculosis, particularly for the determination of superficial foci, which so readily bring on pleurisy or pneumothorax, as also for determining the extent of an acute pleurisy, pericarditis, or peritonitis. It is for me a matter of regret that this method, which, in association with the fixing of the limits of the organs by the methods referred to in the foregoing, allows of such an exact differential diagnosis, has made so little headway among our professors and in our practice, and I can not sufficiently urge it on the attention of surgeons occupying themselves with internal operative procedures, with a view to the prevention of their very regrettable mistakes. It is a method which will never be superseded by the Roentgen-ray photography, is simple, demands no practice, and can be immediately applied by every physician, although it must forego the theatrical effect of the X-ray photography. As everywhere else, so particularly in the field of medicine, the simplest methods remain always the best.

Of great importance is the diet in question in the case of toxic albuminuria, and for the treatment of nephritis. I have shown in another work[11] that the toxins from the gastroenteric fermentation and decomposition processes, being excreted by the kidneys, maintain a more or less pronounced irritation of the renal parenchyma, the degree of which, apart from the degree of the fermentation and decomposition processes, is conditioned only by the varying resist-

ance capacity of the parenchyma of the kidneys, so different in individuals. This toxic albuminuria is demonstrable in almost all cases of fermentation and decomposition, although fortunately very often in only just perceptible degree. Most cases of albuminuria, unassociated with affections of the kidneys and urinary passage, have this gastroenteric origin, and are of great importance as weighty and only guides for judging of the resistance of the renal parenchyma in each individual case of disease, and thus again for the prophylaxis of chronic kidney inflammations. The discovery of severer toxic albuminuria (0.005 to 0.01 per cent) calls at once for the permanent inhibition of alcohol, tobacco, coffee, and highly spiced foods, and for the most thorough removal of any (latent) syphilitic affections that may be present, a measure of which the importance and necessity are in direct proportion to the incurability of the chronic nephritis. Both moderate and severe cases of toxic albuminuria, but first and foremost the more trifling cases, improve of themselves under the diet, without any other treatment than that devoted to the primary disease, even if small traces, especially when the fermentations in the stomach and small intestine have been of long duration, remain demonstrable for a long time as secondary effects. But also in the chronic and acute cases of nephritis this diet is indispensible, and a veritable blessing, just so far as any improvement is still at all possible, as precisely the toxins from fermentations and decompositions in the stomach and small intestine, where these are present, affect most disastrously the diseased renal parenchyma, and thus also the loss of albumin in the body.

Here, above all, must we be concerned to avert the grave dangers of permanent irritations of the renal parenchyma, caused by the excretion of gastroenteric toxins, and the effect of the correct diet is seen in that the amount of contained albumin recedes in a short time from 0.6 to 0.2 and even 0.1 per cent, the miliary casts become reduced in number, and, thanks to the increased strength of the heart, the dyspnœa and edema may be reduced, the diuresis relieved, and the general condition, sleep, and appetite improved. Immediately there is the slightest evidence of fermentation in the gastrointestinal canal, no matter how apparently trifling, in chronic nephritis, and above all in acute nephritis, milk, yolk of egg, butter, and fats must be immediately forbidden. In an acute nephritis the persistent condition of irritation of the renal parenchyma, maintained by gastroenteric fermentations and decompositions, may effectively hinder the recovery of the diseased kidneys. Milk, yolk of egg, and butter are, therefore, permissible only where the digestive processes in the gastrointestinal canal are entirely unimpaired, and when a constant watch can be kept on the dimensions of the heart, stomach, and colon, so that on the appearance, or reappearance, of fermenta-

tion and decomposition in the stomach and small intestine, milk, yolk of egg, and butter may be again cut off, as the recurrence of these processes leads immediately, in absolute accordance with law, as numerous careful observations have shown, to a renewed exacerbation of the albuminuria and the increased passing of casts in the urine. The same applies, as I need hardly say, to the grape cure, so popular in chronic nephritis, as indeed to the allowing of fruit of any kind, which has likewise as preliminary condition an entirely unimpaired gastrointestinal canal, free from fermentations and decompositions, but which also demands at the same time a never-ceasing watch over the measurements of heart, stomach, and large intestine.

I further wish to allude briefly to the importance of the diet in cases where, owing to gastroenteric fermentation and decomposition, there is an excess of phosphates in the urine, and increased excretion of carbonates, which rapidly disappear as soon as an improvement takes place in these processes, and which often in severe stages go side by side with signs of irritation in the urinary passage. The same applies to the abnormal excretion of urates, so far as this is due to the increase of uric acid resultant on the disintegration of the body albumen, which, in its turn, is due to the action of gastric toxins, a state of affairs which we so frequently observe in the case of fermentation and decomposition processes associated with pronounced emaciation. Furthermore, the consecutive diseases of the large intestine conduce to the formation of renal calculi, a part of these concretions having probably for their final cause, as investigations prove, the breaking down of the function of the large intestine to eliminate the very insoluble lime, but especially the oxalic acid. It is fortunate in a way, that generally, owing to a contemporaneous achlorhydria, or subacidity of the gastric juice, the resorption of the calcium salts is prevented, or at least rendered more difficult, otherwise the lime concretions in the kidneys would certainly be more frequently met with. The increase of uric acid already alluded to may, as is known, lead to the formations of concretions of the kidneys. Whilst in the case of phosphaturia and uraturia the action of the diet is so quick and certain, in the presence of renal concretions it is of course unavailing, and its whole importance, therefore, lies solely in the prevention, by a prompt and radical removal of these disorders of metabolism, in the timely removal of the gastric trouble, and probably further in the early removal of the infections of the urinary passage, when these have made their appearance.

In the early years of childhood the dietetic treatment is of importance for the prophylaxis and removal of rickets and for the prophylaxis of subsequent dental caries. The entirely, or at least seriously, arrested absorption of lime, caused by the achlorhydria or pro-

nounced subacidity consequent on severe gastric disease, can not fail to have a most unfavorable influence on the development of bones and teeth. It is for this reason that we meet with rickets only in such children as are not fed at the breast, and in whose case, particularly owing to the sugar given, the occurrence of gastric fermentations and decompositions is encouraged, and these processes themselves markedly intensified. The giving of preparations of lime, with a view to combating rickets, does not affect the indicatio causalis, but has rather a disturbing influence on the digestive processes, as is the case with cod-liver oil, and is illogical, seeing that the trouble is not caused by an insufficiency of calcium salts in the food, but by the greatly lessened resorption of the lime. A contributory cause is possibly the impoverishment of the tissue fluids in alkalies consequent on the fermentations and decompositions in the stomach and small intestine, which shows itself in the increased excretion of carbonates already alluded to, as the alkalies for the neutralizing of the resorbed and greatly increased acids of the fermentation and decomposition processes must be drawn from the blood. To what extent the osteomalacia is influenced by the broken-down lime assimilation resulting from chronic gastric trouble, to what extent accordingly the diet can have a prophylactic and ameliorating action, I have, unfortunately, no experience, owing to the lack of material for observation. That this disturbance plays a part, is probable; other changes in the blood and tissue fluids, however, must certainly cooperate, having a solvent action on the lime in the bone tissue. That pregnancy plays a part, in its providing for the necessary supply of lime, is certain and well known.

The increase of uric acid consequent on the action of gastro-enteric toxins is also of importance in lumbago and sciatica, not infrequently met with in gastrointestinal diseases, complications in which Weintraud, too, has observed an increase of the uric acid. A thorough and permanent cure of these troubles is best and most certainly achieved by applying this diet for the dispersion of the fermentations and decompositions in the gastrointestinal canal, which are the cause of the increased formation of uric acid.

The significance of uric acid in gout is very generally recognized. If we adhere to the view already touched on, that the increase of uric acid in the body is brought about by the accentuated disintegration of albumin contained in the body and of the cell-nuclei, we can then regard as the cause of the pathological increase of uric acid, also in gout, only toxic actions, but not excess of metabolism of meat or a one-sided meat diet. The most important and most frequent cause of these toxic operations, not to speak here of infectious diseases, will be found in the fermentation and decomposition processes of the gastrointestinal canal. As the records of investi-

gations show, the increase of urates here is in direct proportion to the severity of the toxic manifestations of the fermentation and decomposition processes (particularly the fermentations resulting in oleic and butyric acids) and to the rapidity with which the emaciation took place. As has been proved by Garrod, Schittenhelm, Brugsch, and Gudzent,[12] in the case of the gouty subject we have to do with a supersaturation of the blood with sodium monourate, which, however, can not be due to a diminished elimination of uric acid by the kidneys, as this elimination by the kidneys is not restricted in gouty patients. The overloading of the blood with uric acid can, for this reason also, in my opinion, only take place as result of the overproduction of uric acid consequent on the pathologically increased disintegration of nuclei and of the albumin contained in the body. The causal treatment of gout must accordingly be directed against the overproduction of uric acid due to toxic influences, and weight must be laid chiefly on putting an end to the processes of fermentation and decomposition by means of a correct diet, which here, needless to say, must not include calf's sweetbread and calf's brains, articles of food rich in purin, whilst the removal of the toxic influences of alcohol and tobacco will be promoted by the diet itself. In the prophylaxis the reduction of the uric acid to the physiological proportion must always be the essential point. The exceptional position which gout takes among the disorders of metabolism is due to the retention and deposition of uric acid in the tissues, leading to palpable pathological-anatomical changes, which again demand a special treatment.

Umber rightly regards this as the primary condition of gout.[13] A nearer-lying cause of this deposition of uric acid is possibly the atony of the peripheral blood vessels, and the reduction of the strength of the heart due to the toxins of the fermentations and decompositions, which is reflected in the complaints of the patient of cold hands and feet. A further cause of the retention of uric acid in the tissues, in addition to the increased difficulty attached to the carrying off of this acid by the blood due to its supersaturation with uric acid, may lie in the decreased alkalinity of the tissue fluids, which has already been alluded to, as a consequence of the accentuated consumption of alkalies required to neutralize the butyric acid, acetic acid, and lactic acid as resorbed products of the gastric decomposition processes, for the blood, as is well known, is able to maintain its almost neutral reaction within fairly extensive limits. Both possibilities, therefore, neither of which is excluded by their reciprocal influences, point to the great importance of the removal of the processes of fermentation and decomposition. On the uric acid, when once its deposition in the tissues is accomplished, and on the pathological-anatomical changes and their removal, when once they

have taken place, the diet is again without influence. Here only such measures can avail as result in rendering soluble the uric acid deposited, making possible its conveyance into the blood no longer supersaturated with this acid, measures, however, which, according to the investigations of His, Paul, and Gudzent,[14] do not include the use of lithia water and alkalies, for the giving of these, as Gudzent rightly remarks, is in direct opposition to the physical chemistry of the blood and of the uric acid itself.

For the same reason the effect of gastroenteric toxins on the atony of the peripheral blood vessels, in reciprocal action with the flooding of the blood with uric acid, may be of a certain importance also for the etiology of chronic rheumatism, and to this may come as further important factors damp, cold dwelling houses, situated near or on the ground, working under similarly unfavorable conditions, and also chronic alcoholism. I found a careful consideration of the complicating gastro-intestinal ailments to exert the best influence on the treatment of this grave and obstinate disease, if accompanied at the same time by a removal of the unfavorable hygienic factors.

A disorder of the body of exceedingly great moment, which may have its origin in gastro-intestinal disease, and which can be removed by diet, is underweight and emaciation.

Excluding the cases where the emaciation was brought on by other ailments, underweight was observed in 82.8 per cent of 605 male cases and in 81.9 per cent of 580 women. There was an underweight of 5 to 9.5 kilograms in 22.9 per cent of males (2.1 per cent in the period of growth) and in 22.7 per cent of females (4.8 per cent in period of growth), an underweight of 10 to 19.5 kilograms in 39.85 per cent of males (5.4 per cent in period of growth) and in 37.8 per cent of females (6.6 per cent in period of growth), an underweight of 20 kilograms and more in 8.1 per cent of males (0.3 per cent in period of growth, 5 cases bedridden) and 12.9 per cent of females (0.3 per cent in period of growth, 16 cases bedridden). Emaciation without other complications was observed in 84.7 per cent of males and in 82.4 per cent of females, viz, 5 to 9.5 kilograms in 36.5 per cent of males (3.7 per cent in period of growth) and in 32.1 per cent of females (5.5 per cent in period of growth), emaciation to the extent of 19.5 kilograms in 22.3 per cent of males (2 per cent in period of growth) and in 24.7 per cent of females (1.4 per cent in period of growth), emaciation to the extent of 20 kilograms and more in 3.1 per cent of males and in 3.79 per cent of females (0.2 per cent in period of growth).

As emaciation and underweight, as is generally known, greatly facilitate the bacillary infections of the body, by diminishing the power of resistance of the latter, and according to the investigations

of M. Ficker,[15] the permeability of the mucous membrane of the intestines for bacteria in cases of starving is increased; and as, furthermore, in accordance with what has been shown in the foregoing, through the destruction of the bactericidal function of the small intestine consequent on fermentations and decompositions the risk of infection by bacteria is greatly enhanced, we see from this the grave danger, in respect to infections, arising from defective alimentation and emaciation resulting from gastrointestinal disease. Various weighty factors operate to give rise to underweight and emaciation, to which I wish to make here only brief reference. The so near-lying causes of lack of appetite, dread of taking food on account of violent pain resulting, vomiting, hemorrhage, and diarrhea, I shall pass over. In spite, however, of good appetite, in spite of apparently normal digestion and evacuation, emaciation may take place, and that as the result of the fermentation and decomposition processes and their consequences. The chemical effect of these is that the food is so split up in consequence of the fermentations and decompositions that it becomes unsuitable for the synthesis to body-building material. The further chemical-pathological effect is that, in consequence of the fermentations and decompositions, the mucous membrane of the stomach and, progressing further, the mucous membrane of the small intestine, and finally of the large intestine, are injured to such an extent that the secretion of the digestive fluids is gravely prejudiced, with the result that, as shown by the examination of the feces, there is more or less severe damage to the digestion of connective tissue, to the digestion of meat, in consequence of injury to the secretory functions of the liver and pancreas, to the digestion of starch and fats, to the digestion of nuclein, and thus to the resorption of the food.

Furthermore, just as the secretory functions of the mucous membrane of the stomach and intestines are injured, so will also the vastly important synthetic functions of the same be damaged, concerning which we can as yet only make conjectures. Their grave injuries are, however, clearly evident in cases where, in spite of the fact that the secretory and resorptive functions of the small intestine appear from an examination of the feces to be entirely, or almost entirely, restored, and other complications, or grounds for the nonoccurrence of an increase in bodily weight, are wanting, there is for a long time, or even permanently, failure of anabolism, this applying particularly to cases in which the fermentation and decomposition processes have been of long duration. The further cause of emaciation, viz, the injury of the functions of the liver and pancreas, due to the effect of the fermentation and decomposition toxins, and which is more or less severe in proportion to the individually varying resistance of the organs, has been already mentioned. Of not less importance, how-

ever, for the condition of emaciation is the disintegration of the albumin contained in the body, already mentioned in dealing with uraturia, caused by the toxic action of fermentations and decompositions in the stomach and small intestine, and furthermore comes the increased secretion of perspiration, as seen in profuse night sweats, the causa movens of which is given by the fermentation and decomposition processes, which use this channel for the elimination of their poisons, the loss of water on a large scale having always a reducing effect on the body. Emaciation is favored further by any more pronounced toxic albuminuria that may be present, by misdirected therapeutic measures, among which may be particularly instanced the use of saline waters and purgatives for combating constipation, with their gravely injurious action on the small intestine, also on the stomach and large intestine, by long-continued washing out of the stomach, etc.

I wish to emphasize here that forced alimentation in cases of (so frequently latent) gastrointestinal disorders and diseases, resorted to as it so often is, to relieve conditions of weakness and emaciation, is entirely mistaken, as it can at the best only temporarily increase the weight and must invariably accentuate the fermentation and decomposition processes, through the overtasking of the diseased mucous membrane of the stomach and intestines, but particularly on account of the mistakes made in the selection of foods. In consequence of this, again, all the severe toxic manifestations are accentuated, and the ruin of the stomach and small intestine functions becomes more complete, as I have often enough been able to observe in the case of patients who had gone through such a treatment of forced alimentation in sanatoria. The stomach and small intestine, however, tolerate least of all a treatment based on such faulty hypotheses. It is not the increase in the weight, and with this the removal of the underweight as a manifestation of the disease, but rather the radical removal of the cause of the underweight, which we should regard as the sole object worthy of our striving after. This accomplished, the increase of weight will follow of itself, always assuming that the functions of the stomach and small intestine have not been too long and too severely injured. The same applies to all tonics and restoratives, the giving of which is justified only when they are (1) free from all substances which give rise to fermentations and decompositions, and (2) so easily absorbed that they do not make too heavy demands on the mucous membrane of the stomach and small intestine. Here, too, only painstaking examinations, particularly of the faeces, can guard us from wrong therapeutic measures, when we have to do with extreme cases of underweight. Of particular moment are the injuries resulting from gastrointestinal diseases which have been in existence from earliest childhood and which have

resulted in a serious and continued condition of underweight, in the stunting of the whole body, and, in the presence of severe toxic conditions, even in the retarding of the mental development. In proportion to the severity of the injuries to the stomach, small and large intestines, the greatest caution is to be exercised in judging of the prognosis.

Similar considerations will apply also in anemia and its dietetic treatment, a complication which, more or less strongly stamped as aftercondition of the fermentations and decompositions, is not less common than underweight or emaciation. In the so extraordinarily frequent cases of latent gastrointestinal ailments, anemia, in association with emaciation and underweight, forces itself to the forefront to such an extent that the primary disease, that of the stomach and intestines, is overlooked and the anemia regarded and treated as independent complaint. This, as in the case of emaciation, can never lead to a permanent and speedy success, seeing that the cause of the anemia works on unabated, or is even aggravated by the use of iron preparations, as are also the fermentations and decompositions. For, leaving the hemorrhages as cause out of consideration, proceeding as they do, whether acute or latent and chronic, from the lesions of the mucous membrane, the cause is found here again in the results of the processes of fermentation and decomposition. As contributory cause comes the circumstance that the resorption of the iron in the food is rendered difficult or prevented, owing to the injury of the mucous membrane of the stomach and small intestine. The predominating cause, however, lies in the toxic effects of the fermentation and decomposition processes, consequent on which follows the disintegration of the red blood corpuscles, and so the increased elimination of biliary pigment and urobilin, the deposition of pigment in the skin, as seen in the grayish yellow color of the skin in such patients. But the new formation of the red blood corpuscles is checked by the more or less serious injuries caused to the blood-forming organs by the influence of the toxins from the processes of fermentation and decomposition.

In women we have, to complete the viscious circle, menorrhagia, which has been shown elsewhere [16] to be sometimes due to the paralizing effect of the toxins of the fermentations and decompositions on the uterine vessels. The symptomatic treatment of such cases of anemia with ferruginous remedies is as illogical as it is useless and harmful, as I have shown at more length elsewhere.[17] Only the dietary method of cure, full allowance being made for the primary disease, in contradistinction to the symptomatic treatment, can result in the speedy and lasting removal of the primary disease, at the same time putting an end to the anemia without the use of iron preparations.

All authorities agree in attaching the greatest importance to the dietetic treatment of diabetes mellitus. This treatment is here, as in gastric disorders, diarrhea and nephritis, an absolutely unyielding necessity, but has been hitherto, in this disease as in the gastric ailments, built up to some extent on entirely false suppositions, its nature, its causality, not having hitherto been correctly grasped. I have pointed out elsewhere[18] that the cause of diabetes mellitus may lie in the circumstance that the parenchyma of the liver, owing to the damaging action of the toxins from the fermentations and decompositions, is rendered incapable of converting the levulose of the blood of the vena portae into glucose. But for diabetes to appear in gastroenteric fermentations and decompositions there must of necessity exist a weakness, or a severely reduced resistance, of the parenchyma of the liver, exactly analogous to the producing of a more pronounced toxic albuminuria in the case of the weakened parenchyma of the kidneys; otherwise every case of fermentations and decompositions existing over a long period would show diabetes as a secondary manifestation, which, however, is by no means the case, exactly as we saw in the severe albuminuria. This weakness of the parenchyma of the liver, as in the case of the renal parenchyma, may be inherited, or, as the result of previous disease, particularly syphilis, or other ailments, it may be acquired. As weighty conditions working together to produce diabetes mellitus, there are thus two contributory causes necessary, the causa disponens and the causa movens, the toxins of the fermentations and decompositions. But the removal of the causa movens alone, and this is of the utmost importance for the treatment of diabetes mellitus, is sufficient to effect a cure of this complication. The causa disponens, however, explains the tendency, which invariably remains behind, to relapses as soon as the causa movens again becomes operative.

In this way is given also the distinction so exceedingly important therapeutically between these two weighty factors in the etiology of the manifestations of disease, and of the diseases themselves. Entirely in keeping with this is also the behavior of the process of sugar excretion in the urine; it disappears entirely with the correction of the processes of fermentation and decomposition in the stomach and small intestine, to appear again, however, in what may almost be termed absolute conformity with the law of cause and effect, directly fermentations and decompositions again make their appearance, in consequence of too early broadening of the diet, or as a result of mistakes in the latter, such as warmed-up food, etc. We observe this immediate reappearance of sugar in the urine—and this is the cardinal point in the therapy of diabetes mellitus—just so long as no tolerance of fats and sugars is created in the stomach. The impossibility of establishing this tolerance in the stomach (fortunately

a very rare contingency) entails a rigorous dieting for the remainder of life. My careful observations of severe diabetes cases of long standing, which have become more numerous since my previous publication,[19] could not but confirm me in regarding diabetes mellitus simply and solely as a disorder of the parenchyma of the liver and its functions referred to, brought about by the toxic action of gastro-enteric fermentations and decompositions of many years' standing; for I have never seen a single case of diabetes mellitus in which these processes were not in evidence and in which, simply through putting an end to these processes, the sugar in the urine was not speedily and certainly removed, in spite of an entirely unrestricted administration of amylaceous foods, even after 10 to 15 years' duration of the disease. I am fully convinced that with this I have discovered a complete solution of the hitherto unsolved problem of a certain and permanent cure of diabetes mellitus, that grave and fateful disorder, and here, too, in the causal therapy which alone I have in view. With this, diabetes falls from its position as an independent disease. The causal treatment of diabetes is the more important that the diabetes diet has hitherto been only symptomatic; it was a diet which many patients could not support, one under which they lost weight considerably, the abstaining from amylaceous foods being the most unpleasant and most mistaken sacrifice. The reason for the emaciation was that, apart from the continuance of the toxic influences, the process of fat resorption and meat digestion in the small intestine were severely injured by the primary disease, and with the permanence of the latter could not but remain injured, whilst all the other causes of the emaciation already mentioned worked on unabated. The diet hitherto has only artificially reduced the excretion of sugar. Furthermore, owing to the increased amount of fats given to make up for the loss of calories involved in the cutting off of carbohydrates, the processes of fermentation and decomposition were only aggravated; and as precisely the products resulting from the decomposition of fat and butter are the most dangerous and most toxic in their action, the dangers accompanying the effects of the toxins on the body, heart, blood, but especially the entire nervous system, were enhanced.

Thus there was achieved the exact opposite of what the causal treatment accomplishes, the aim of which is, first and foremost, the complete removal of the fermentations and decompositions, the relief of the grave gastrointestinal disease, the repairing of the severe injuries inflicted by the latter on the heart and the cerebral functions, and which, in a word, strives after complete recovery. For this reason the pronounced neurasthenic condition of diabetics treated on these faulty symptomatic lines, under the diet hitherto usual, remained on, as also the insomnia and weakness, the patients being

more or less incapable of any great mental or physical performance, retaining their cardiac troubles and respiration difficulties, their profuse sweats, and the so frequent furunculosis consequent on the severe injury of the bactericidal function of the small intestine, which not infrequently brought with it grave risks for the sufferers. The inclusion of green vegetables in the diabetes diet brought with it the aggravation of the diseased condition of the mucous membrane of the stomach and small intestine, but particularly of the mucous membrane of the large intestine with its lesions, and the result in not a few cases was severe diarrhea. Owing to the too heavy increase of meat foods, the functions of the diseased mucous membrane of the stomach and small intestine were overtasked, while the entire process of assimilation, already suffering heavily under the effects of the toxins of the fermentations and decompositions, was still more unfavorably influenced. The entire gain of the old diabetes diet, the suppression of the excretion of sugar in the urine, was only insignificant, not to say illusory, when set against the serious dangers to which the permanence of the fermentation and decomposition processes exposed the whole body, and which led finally to the grave issues of the hitherto incurable disease. Therefore our first task henceforth must be, not the removal of a symptom, the excretion of sugar in the urine as result of the seriously injured function of the liver, but the relief of the primary disease, the removal of the causa movens. But the primary disease explains to us of itself also the appearance of the other severe disturbances in diabetes mellitus, just as the removal of the primary disease guarantees of itself the removal at the same time of these disturbances, particularly in the central nervous system, thus giving promise of complete recovery, an achievement to which the diet in vogue hitherto, being altogether faulty, only symtomatic, adapted only to a disorder, not to the primary disease, could never rise.

Merely for the sake of an apparent success, the primary disease, hitherto overlooked, or regarded as a disorder of only secondary importance, with all its dangers, was aggravated by the symptomatic, dietetic treatment of the diabetes as practiced in the past, for the simple reason that this diet was a contradiction of the laws of nature. I must here again declare myself opposed to the proposal that has been made in other quarters, by washing out the stomach to lessen the elimination of sugar in the urine; I consider this procedure justified only once and that in coma diabeticum, in order to effect a cleansing of the chief center of the fermentations and decompositions, the stomach, and to counteract the poisoning of the blood by the acetic acid and fatty acids. But then must commence the diet and medication, which must here, too, be only such as are appropri-

ate to the primary disease. The mere irrigation of the stomach, as already stated, can never remove, permanently and completely, the processes of fermentation and decomposition in the stomach and small intestine; this can follow only from the removal of the disease of the stomach and small intestine by correct dieting, for if this diet is only maintained long enough, it is of itself able to render the stomach tolerant of fats and sugar, a condition of the utmost importance for the permanent cure of diabetes, and to restore the stomach's function of keeping down fermentations and decompositions, neither of which can be achieved by irrigations of the stomach, which, as has been shown, only result in a weakening of the mucous membrane of the stomach.

A very special consideration and appreciation does this diet merit in cardiac disorders brought on by gastric ailments, for the reason that these disorders, without the diet in question, under the methods of treatment of the past, could not be removed, but could at the most be only ameliorated for a time, and also because we are concerned here with an extremely important organ. First of all must be mentioned the so-called nervous cardiac disorders, and first of these palpitation, with or without some more closely related cause, such as excitement or overexertion, then also angina cordis, tachycardia, arhythmia, and the reflex cardiac pains, all of which, as I have shown elsewhere,[20] have for their moving cause the gastric disease, or irritations of the gastric lesion. Of greatest importance, however, is this diet for the treatment of cardiac weakness and cardiac dilatation, which, as shown by observations recorded during the past 25 years, are due simply and solely to the toxic effects of the fermentation and decomposition processes on the cardiac muscle, as was set forth in an earlier part in discussing the increase of the heart width as reliable indicator of gastroenteric fermentations and decompositions. Granting strict obedience on the part of the patient, it is possible in from four to six weeks to disperse the gravest conditions of cardiac weakness and cardiac dilatation, as long of course as the cardiac muscle is involved in no degenerative processes. Nowhere does the marvellous recuperative power of the organism arouse our wonder to such an extent as in the case of the heart, when we see cardiac dilatations, measuring in transverse section up to 25 and even 28 centimeters, reduced to 7 or 8 centimeters, and this within such a short space of time. Hydro-therapeutics, massage cures devoted to the heart, or other therapeutic or medicinal remedies are absolutely unnecessary, even disturbing, for the removal of the primary, the gastro-intestinal disease. A cardiac weakness which had sunk to 9 or 10, or even lower, on Sahli's manometer, improved at once, and of its own accord. In these cases of extreme cardiac weakness, the heart regains in four, at the most five, weeks its normal strength. Arhythmia also,

which, according to observations and as shown elsewhere, (l. c.), is generally a result and symptom of the exhausted condition and severe atony of the heart, and which for this reason imperatively demands absolute rest of body and mind, disappears in time spontaneously, and the frequency of the pulse, which under the toxic influence of the fermentations and decompositions had gradually increased, or presented the type of bradycardia, as a sign of the exhaustion of the cardiac muscle, becomes again entirely normal. The cessation of accidental murmurs, which are by no means uncommon in the case of more extensive cardiac dilatations, is also to be observed.

A fact which I think worthy of mention is that cardiac dilatations of lesser, even those of medium severity, generally remain latent (unaccompanied by pain), or at the most give rise at times to palpitation, which is generally regarded as of nervous origin. These cardiac dilatations lead, however, to premature exhaustion of the strength of the heart, on account of the much more unfavorable conditions under which it works, easily explained by its changed physical conditions. These dilatations unfold their gravest dangers in narcosis, in intermittent feverish illnesses, particularly in pneumonia, and typhus, when taking cold baths, or when indulging in unusual physical exertion, and are in fact the cause of the sudden arrest of the heart's action, cardiac paralysis, following on severe mental shock, or on the overtasking of the heart already referred to. Just as fateful are these cardiac dilatations in complications involving a permanent overstraining of the heart, such as arteriosclerosis, contracted kidney, but above all in the presence of valvular defects of the heart, for the reason that under these conditions failure of the heart's strength sets in much quicker, with all the consequences which that implies, the manifestations of passive congestion, oedema, etc. The timely discovery and prompt removal of what is the weightiest and most common cause of a compensatory disturbance of cardiac defects, in atony of the heart and cardiac dilatation, following on fermentations and decompositions of the stomach and small intestines, is far more important, and above all far more fruitful of result than all the medicinal treatment of valvular defects of the heart with digitalis and other medicaments. Here, too, nothing can take the place of correct diet, which has a directly life-saving action; for the increasing of the heart's strength and removal of the oedema, the reduction of the cardiac dilatation, and with this the return of favorable conditions for the heart's functions (without the dispersion of the fermentations and decompositions), by the usual heart remedies alone, is de facto an impossibility, as a great number of most careful investigations have shown. No one has hitherto directed attention to this most important point in the treatment of defects of the cardiac valves. As

these cardiac remedies, when administered through the stomach, have generally an unfavorable influence on the functions of the stomach, already in a very unstable condition, I have, during the past 10 years, more and more discontinued their use, even in severe cases of compensatory disturbances.

In taking this course, the results obtained, in cases which had been treated elsewhere for a long time in vain without consideration of the gastroenteric fermentations and decompositions, have convinced me that compensatory disturbances, the incompetency of the cardiac muscle in defects of the heart, owes its origin always to the associated disease of the gastrointestinal canal, that is to say, to the fermentations and decompositions taking place there, and that with the dispersion of these processes the cardiac defect at once falls back into its latent condition, in which it causes no inconvenience—this of course so long as no degenerative processes are in evidence. I have found, moreover, that the impulse to these compensatory disturbances of valvular defects of the heart is given to a very great extent by infectious diseases, particularly by influenza, on account of the severe injuries which it inflicts on the functions of the stomach, also of course by alcoholic excesses, and by serious mistakes in diet. So long as no degenerative processes of the cardiac muscle are at work, the dispersion of the gastric fermentations and decompositions allows of the complete removal also of cardiac dropsy, and observations show that arteriosclerosis and advanced age prove here no hindrance. Of great importance, too, is the prompt treatment of gastric dilatations of the heart, particularly in the presence of valvular defects, in order to prevent the degeneration of the cardiac muscle, in which other factors, such as exhaustion of the cardiac muscle, alcohol, syphilis, etc., play a part. On account of the influence of the toxins of the fermentations and decompositions on the atony of the vascular muscular apparatus already alluded to, which atony manifests itself, besides, in the complaints of cold hands and feet, also in a tendency to chilblains, etc., the cases of menorrhagia, so frequent in gastrointestinal diseases, become susceptible to a dietary treatment, assuming of course that they are not conditioned by local affections.

As patients so very often suffer at the same time from gastrointestinal disease and also arteriosclerosis, on account of the frequent occurrence of these troubles, it is exceedingly difficult to say, in the lack of success attending the treatment of arteriosclerosis, in contradistinction to almost all the complications already mentioned, whether there exists a causal connection between these two diseases. It should not be overlooked that we very frequently meet with arteriosclerosis in persons suffering from gastric complaints unusually early, between the ages of 30 and 40, also in women, in whose case alcoholism and to-

bacco have only exceptionally, and syphilis still less frequently, to be reckoned with. According to investigations extending over many years, the toxins of fermentations and decompositions can not constitute the causa movens of degenerative processes in the organs. I do not, however, for one moment question that they weaken the resistance of the organs, and thus create, for other toxins with degenerative action, and in the circulatory apparatus for the effect of overexertion, a causa disponens for degenerative processes. In this respect a strict dieting and the abstaining from overexertion of the body are of exceedingly great prophylactic importance in arteriosclerosis, and, where the latter has once set in, for the prevention of the too speedy progress of this degeneration, which is, and will remain, inaccessible to all other treatment.

With regard to the lungs, there comes in question the dietetic treatment of asthma, so far as it is conditional on cardiac dilatation, a matter which I have already dealt with elsewhere.[21] This cardiac dyspnœa disappears just as quickly as does the cardiac dilatation itself. Here, too, arteriosclerosis and advanced age are no obstacle to the success of dietary treatment just as long as there is no degeneration of the cardiac muscle. In severe cases, with combined old age, arteriosclerosis, toxic albuminuria, and to a certain extent also albuminuria due to passive congestion, oedema and ascites were observed, which, nevertheless, under dietetic treatment, with medicines checking fermentation, disappeared of their own accord. Accidental complications with emphysema of the lungs, diffuse bronchitis, may render the dyspnoea unusually distressing, the latter, however, improving considerably with the removal of the gastric cardiac dilatation and cardiac weakness by means of a correct dietary treatment, so that here, also, this treatment may prove a veritable boon. In the work referred to (l. c.) I discussed also the removal, by healing the gastric lesion, of angina pectoris, of difficult respiration in the presence of high-seated gastric lesions, and the manifestations of irritation in the region of the lungs, to all of which gastric lesions, by reflex action, may give the moving cause.

Of far greater importance is the relation of the diseases of the gastrointestinal canal to the etiology of tuberculosis, particularly pulmonary tuberculosis. I have for 25 years closely investigated this relation, and collected copious material, which it is my intention shortly to publish. I wish to sum up in the following axioms the more important results of these studies, as they are of particular importance for the prophylaxis of manifest pulmonary tuberculosis, and for this reason may deserve mention at this congress.

(1) In all these 25 years, out of a vast number of cases, I have not seen a single case of manifest pulmonary tuberculosis (that is to say, tuberculosis associated with disintegration of the lungs follow-

ing on mixed infection) in which there was not present extensive disease of the gastrointestinal canal, which, by careful examination, usually shows itself far better during life than on the dissecting table. This disease included almost always gastric lesion, invariably gastrointestinal fermentation and decomposition processes of long standing, with generally extensive injury of the functions of the small intestine, particularly extensive injury of its bactericidal function, injury of the functions of the large intestine, with, very frequently, lesions of the latter, furthermore coincident dilatation and weakness of the heart, and, going parallel with the latter, enlargement and atony of the digestive tract. Side by side with the generally latent lesions of the large intestine, and with the latent appendicitis, there was frequently also tendency to diarrhoea, and that in all its grades up to the severest forms of this complaint. I can therefore de facto not conceive a pulmonary tuberculosis unaccompanied by the more or less serious changes in the digestive tract referred to.

(2) By careful interrogation of the patient I have always been able to establish the fact that in a gastric lesion the reflex manifestations of the latter, as early symptoms of the lesion, made their appearance much sooner than the signs of the manifest pulmonary tuberculosis; that these manifestations had been in evidence as early as in the school days, and that the manifestations of the gastric fermentation and decomposition processes, as bearing on the motor function of the intestine, on the cardiac function, the cerebral functions, and furthermore, the secondary anaemias, emaciation and underweight, also invariably preceded the appearance of the manifest pulmonary tuberculosis. Furthermore, examination of the feces showed that the functions of the small and large intestines, and the connective tissue digestion, were always injured in a manner such as is met with only in gastrointestinal ailments dating back to the years of childhood. All these are manifestations of disease which indicate to the observant investigator the presence of (latent) gastrointestinal disease, which, promptly removed, together with the primary disease in childhood, would prevent the outbreak of the manifest tuberculosis. The timely recognition of these manifestations of disease, and their prompt removal, would constitute the most effective weapons with which to combat the outbreak of manifest tuberculosis.

(3) Manifest tuberculosis will result generally when the gastrointestinal disease present is aggravated by severe injuries or when there is a relapse of a gastrointestinal disease which had subsided. Particularly frequently does influenza inflict injury on the gastrointestinal disease, as already mentioned, both by its effect on the gastric lesion, and also in respect to the accentuation of the fermenta-

tions and decompositions, and it is these grave injuries which then, analagous to the compensatory disturbances in defects of the cardiac valves, give the first impulse to the outbreak of manifest pulmonary tuberculosis whereby, of course, also the injuries which the influenza inflicts on the lungs cooperate. A similar action is observed in measles and whooping cough. Moreover, the hemorrhage of a latent tuberculous focus of the lungs or the perforation of such a subpleural focus into the pleural cavity or the encroaching of the inflammation of such foci on the pleura and the pleurisy to which this encroachment gives the moving cause, so common in latent gastric diseases, may all conduce to the outbreak of the manifest tuberculosis.

(4) All patients with gastrointestinal complaints exhibited without a single exception residues of subsided tuberculous disease of the lungs, i. e., centers of thickening, and a great number of these patients—at a rough estimate 96 per cent—had also foci of latent pulmonary tuberculosis, with the characteristic reactions to tuberculin in the cases where these could be undertaken.

(5) In all cases of latent pulmonary tuberculosis the catarrhal manifestations of the latter invariably improved immediately the gastrointestinal fermentations and decompositions were removed and, with the healing of the gastrointestinal disease, were also completely healed whenever these cases could be long enough controlled.

(6) It was established that in cases of commencing manifest pulmonary tuberculosis, in spite of preceding hemorrhage of the lungs, and even here and there in spite of the presence of mixed infection and fever, although not of long standing, the manifest pulmonary tuberculosis was arrested and finally completely cured as soon as the gastrointestinal disease was removed. At the same time an increase of body weight set in, although generally very slowly, but at least the further progress of the emaciation was prevented, in which latter cases the injuries to the functions of the stomach and small intestine, resulting from the fermentations and decompositions existing since childhood, and probably also the injury of the synthetic functions of the mucous membrane of the digestive canal, were too severe to allow at that stage of an increase of body weight.

(7) In the cases with cavities and disintegration of the lungs there was possibly neither an improvement of the pulmonary disease nor a complete cure of the gastrointestinal trouble, only at the most some improvement of the latter by dietary treatment. Nothing can then be hoped for from a dietetic treatment of the primary complaint, and least of all from a treatment by medicaments of the gastrointestinal disease. Against the latter method of treatment here I can not warn too strongly, unless it should be necessitated by diarrhea. To what extent a dietary treatment is called for depends entirely upon the degree of the fermentation and decomposition processes and of the

disturbances dependent upon them; also upon the local troubles of the primary disease, taking into consideration the condition of malnutrition.

(8) By careful examination of patients of all ages the fact could be established that the first tuberculous infection of the lungs, and thus their induration, must take place in earliest childhood, in the first or second year, to which result, I believe, other investigators have also come.

(9) The intensity of this infection of the lungs, and so the extent of the foci of the diseased lungs, in this early age is, according to my careful investigations, simply and solely dependent upon the manner of feeding, upon the severity of the gastrointestinal disorders due to improper feeding, or to foolish mistakes in diet after the child has been weaned. This is in such strict accordance with laws that from the extent of the pulmonary indurations found in patients in their later years may be concluded with almost absolute certainty whether, and for how long, the patient in question was suckled in his first year, but especially whether more or less severe gastric disease had been present in the first or second year. The fact that all children artificially fed in the first year, or after having been fed at the breast, in consequence of an irrational diet, in which sugar particularly plays a most harmful part, suffer in the second year for the first time from gastric complaints, is alone sufficient to explain the fact of the first tuberculous infection constantly occurring at this age. I have also been able to determine at this age, by careful examination of the lungs during the course of the gastric disease, a more extensive pulmonary affection, manifesting itself in fine râles, in a shorter sound in the upper region of the lungs, and in light feverish symptoms.

(10) At this first invasion of the lungs those parts of the lungs, as is known, suffer the most extensively and most severely in which the respiratory movements of the thorax are least. The internal respiration of the blood has a decidedly hindering effect on the extension and the intensity of the infection with tubercle bacilli. For this reason, (*a*) both the apices of the lungs and (*b*) those parts of the lungs under the scapulæ, especially the axillary portions, are invariably affected; (*c*) the tuberculous pulmonary changes on both sides, as records show, are never equally extensive. This is due solely to the fact that (*d*) the side most affected is invariably the one on which the child is accustomed to sleep. From the predominating of the pulmonary changes on one side we can always safely venture on the conclusion on which side the patient in question had been accustomed from childhood to sleep.

(11) This first infection of the lungs with tubercle bacilli may, parallel with the healing or the ameliorating of the gastric complaint

in the first or second year of age, take on a considerable improvement, following on the well-known cicatrised thickenings, but are only exceptionally entirely healed; the records of careful investigations show that, in individuals of all ages, almost invariably, at all events in the case of patients with gastric or gastrointestinal complaints, there remain behind more or less extensive foci, particularly in the upper scapular regions. These are the latent tuberculous foci, with more or less pronounced catarrhal symptoms in keeping with the auscultatory result, whereby the patient is not troubled by coughing, is not sensible of any manifestations of disease that would allow us with certainty to assume the continuance of the tuberculous processes. Side by side with this we find very frequently the so-called nervous disorders already mentioned, anemia or malnutrition, change of complexion, varying feeling of strength, and other indications, which all point in childhood and the years of development to the presence of latent gastrointestinal disease.

(12) As favoring the transition from latent to manifest tuberculosis, there invariably operates an hereditary predisposition, with which, however, invariably goes side by side an hereditary predisposition to gastrointestinal disease, particularly where we have hereditary predisposition on the maternal side, on account of the incapacity of such mothers as a rule to suckle (breastfeed) their children. A further predisposing influence is exerted by the everywhere well-known unfavorable social and hygienic conditions, particularly those connected with the occupation, which exert also an unfavorable influence on the gastrointestinal disease present at the same time, and furthermore by other weakening diseases, which invariably also at the same time aggravate the gastrointestinal complaint. It is to these factors that is to be ascribed the fact that pulmonary tuberculosis becomes manifest particularly in youth (the years of development). After all my observations, however, and in spite of the presence of hereditary predisposition and the hygienic and social influences alluded to, I regard the simultaneous cooperation of gastrointestinal disease as the causa movens of this transition to manifest tuberculosis as essential.

(13) The extraordinary intimate association of two diseases, the gastrointestinal disease and the pulmonary tuberculosis—another such is not known to me—can only be explained by the fact that, on account of the temporary or even permanent destruction of the bactericidal function of the small intestine in earliest childhood, an invasion of tubercle bacilli through the diseased intestine is rendered possible, or that, owing to the excretion of the gaseous toxic products from the fermentation and decomposition processes, which, as has been shown elsewhere,[22] takes place for the most part through the lungs, but also owing to the toxins of these processes

circulating in the blood, the power of the lungs to repel an invasion of tubercle bacilli through the air passages is for a time suspended. It is possible, however, that both factors favor at one and the same time an invasion of the lungs. For these factors there speaks the persistence of the latent tuberculosis in patients suffering from gastrointestinal complaints with fermentation and decomposition processes, as also particularly the extinguishing of foci of latent tuberculosis with the healing of the gastrointestinal disease, the increasing of the catarrhal manifestations of latent tuberculosis coincident with the aggravation of the fermentations and decompositions resultant on errors of diet during the treatment, and furthermore, the very favorable influence of the healing of the gastrointestinal disease on the commencing manifest pulmonary tuberculosis. Furthermore, a certain parallelism of the lesions of the large intestine with the latent tubercuIous foci forces itself upon the attention of the observant investigator.

(14) The mixed infection in manifest tuberculosis, everywhere recognized as a most dangerous issue for the rapid destruction of the lungs, is probably also due to the destruction of the bactericidal function of the small intestine to some extent at least. It is probably analogous to the furunculosis of the skin in diabetes mellitus, already alluded to, consequent on the destruction of the bactericidal function of the small intestine and the immigration of pathogenic bacteria in the skin. On the other hand, the causal dependence of diabetes on the fermantation and decomposition processes of the stomach and small intestine already dealt with, explains the so frequently observed issue of diabetes in pulmonary tuberculosis.

From all these observations, experiences, and results we see both the extraordinary importance of correct dietetic treatment for the healing of latent and of commencing manifest pulmonary tuberculosis, as also particularly the great importance of this dietary treatment in earliest childhood for the exceedingly important prophylaxis of a later issue of the latent tuberculosis in manifest tuberculosis, as also for the prophylaxis of a tuberculous infection in general. As the one and only correct food and diet in the first year of life is the child's natural food as provided by nature, the best protection against tuberculosis will be afforded by the suckling of the child till the completion of the first year, and then by correct, rational, most cautious feeding in the following years, that is to say, such as aims at keeping away fermentations and decompositions and gastrointestinal disease in general, as also by a careful transition to the ordinary diet. Through this, not only shall we prevent, as far as in us lies, the invasion of the infantile body by tubercle bacilli, but we shall also create, in the strengthening and maturing of the child's

gastrointestinal canal, an effective protection against the primary ailment—the gastrointestinal disease. The instructing of the people by means of pamphlets distributed at the time of marriage emphasizes already the vast importance of suckling; instruction should, however, be given also—and this is almost of equal importance—with regard to the correct feeding and rearing of the child during the next two to three years, with a view to the prevention of gastrointestinal complaints. A careful watching over the gastrointestinal canal in the later years of childhood, the immediate and proper treatment of even trifling gastrointestinal disorders, the correct interpretation of anæmia, of the reflex irritation symptoms of latent gastrointestinal disease on the part of the physician, to emphasize this once again, the removal of latent gastrointestinal disease during the years of childhood are, then, just as important for the prophylaxis of manifest pulmonary tuberculosis as are the selection of a suitable calling, gymnastics of the lungs, singing—in a word, the increased exercise of the lungs. Also in tuberculosis of the lymphatic glands, the scrofula of children, an important part is played by the gastrointestinal disease always present, at the same time the early dental caries almost always present, as also the infection of the lymphatic glands with tubercle bacilli proceeding from carious teeth. Here, too, the most fruitful soil for the thriving of the tubercle bacilli is afforded by the malnutrition, the anæmia, the reduced power of resistance consequent on the gastrointestinal disease, but also certainly by the altered mixture of the fluids of the body due to the toxins of the fermentation and decomposition processes of the gastrointestinal canal. I wish to mention also that the good results which have hitherto been obtained empirically from rest cures in the treatment of tuberculosis in my opinion are chiefly due to the fact that these rest cures benefit first and foremost the primary disease—the gastrointestinal ailment—whilst for the healing of any insignificant remains of latent tuberculosis, after the healing of the gastrointestinal disease, just the aforementioned increased movements of the lungs are of the greatest advantage, as the records of investigations show.

Of great importance is the diet, further, for the removal of migraine, headaches, so far as they are dependent on irritations of a gastric lesion, vertigo, and all the other often tormenting reflex manifestations of gastric lesions, especially in the domain of the sight, hearing, etc., as described at length elsewhere.[22] I wish once again to refer to the injuries resulting from the symptomatic treatment of these extraordinarily common complaints that has been practiced hitherto, a treatment which can only temporarily alleviate or suppress, but which can never effect the permanent cure possible to

the causal treatment, seeing that the cause always continues to work on, whereas the causal treatment removes the cause. I wish to draw attention to the injuries which must result from the medicinal, symptomatic treatment of the past, owing to the importation of foreign substances which are by no means indifferent for our metabolism, to the injurious effects which these substances must have on the primary disease, the gastrointestinal disease itself, which they generally aggravate instead of mend. But above all I wish to point out that, through the one-sided treatment of a symptom, all the grave injuries which the primary disease inflicts upon the rest of the body are left out of consideration in the scheme of cure. This constitutes the most dangerous feature of a symptomatic treatment when we have to do with so serious a disease, which, as in the case of gastrointestinal disease, extends its harmful influence over the entire body.

This diet is, moreover, of exceedingly great importance for the treatment and removal of morbus basedowii, of which the primary disease, in all the cases that have come under my treatment, was a lesion of the stomach, with consecutive disease of the intestinal canal consequent on the advancing fermentation and decomposition processes. The severe atony of the heart and cardiac dilatation, the tachycardia, sleeplessness, prominence of the bulbi, the changes of the thyroid gland, so far as these are not conditional on self-subsisting independent disease of the latter, and the other symptoms, disappear quickly and completely. It may be that here, too, as in the case of diabetes mellitus, there is present also a functional disturbance of the thyroid gland under the toxic influence of the fermentation and decomposition processes, which gives to the aspect of the disease these peculiar characteristic variations. I can here only warn against forced alimentation with its injurious action already alluded to, above all against the use of thyroid gland preparations, the internal use of iodine preparations so fateful for the gastrointestinal disease, as also against surgical interference, so long as no tracheal troubles are present. The causal treatment, i. e., the treatment of the gastrointestinal disease, the rest treatment, so indispensable both for the primary disease and the cardiac complications, are entirely sufficient to bring about a cure.

In another extensive and not less important domain, that of the disturbances of the cerebral functions, and of certain psychical disturbances, so far as these, as discussed elsewhere, have their causa movens in gastric or gastrointestinal disease, the dietetic treatment is indispensable. The latter is more important than all medicinal, all physical symptomatic treatment. With reference first of all to neurasthenia,[24] I can under no circumstances regard this exactly, as

in the case of anemia, as a self-subsisting ailment. It is always a result of more or less severe toxic conditions, and its degree is for the most part dependent on the intensity of the toxic factor, but also on the highly important causa disponens, the hereditary validity and power of resistance of the nervous system. The whole foundation aim of our therapeutics here is to fathom the cause of the toxic changes, and, where possible, to remove them, but not to combat the neurasthenia, as has hitherto been done, symptomatically, which is like trying to empty a river with a pail, and which on logical grounds must be unavailing. Every case of neurasthenia in which even a trifling cardiac dilatation and the already described parallelism of stomach and colon dilatation can be discovered as reliable indicator of gastroenteric toxic action must not be otherwise treated dietetically than the primary disease itself, the gastric or gastro-intestinal disease. Bodily rest, this extraordinarily weighty factor in the treatment of the primary disease, is also in neurasthenia, as is well known, of greatest importance, also inasmuch as the products of metabolism exert a decidedly intensifying influence on the heightened psychic motor and reflex excitability; but also mental rest, as is generally recognized, is of not less importance. All excitement, mental shock, as has been shown elsewhere,[25] has an aggravating influence on the primary disease, on the gastric lesions, as also on the fermentations and decompositions of the stomach and small intestine, and, further, as is well known, accentuates the neurasthenia. Allusion has been made elsewhere [26] also to the heightened motor excitability, as it shows itself in gastric diseases in the cardiac muscle, in the symptom of twitching, with or without the sensation of falling, and in a lesser degree in the twitching of single muscles, especially in the region of the *N. facialis* and the motor branch of the *N. trigeminus*. This heightened motor excitability, likewise due to gastroenteric toxins, has great casual significance in epilepsy and chorea, which also on this account become susceptible to a dietetic treatment, particularly with a view to checking the seizures in epilepsy. The dietary treatment, which here especially must unconditionally be supported by bodily, and above all psychic, repose, is far more important than the treatment of epilepsy with bromine medicaments.

All these unfortunately only accentuate the fermentation and decomposition processes in the stomach by injuring the chemical gastric functions and, indeed, by long use actually give rise to these processes where they are not yet present, by weakening the stomach's tolerance of fats, and therefore of milk and eggs, also of sugar and all foods containing sugar. I am, however, convinced from careful observations and therapeutic results that the causa movens of epileptic seizures is not infrequently given by centripetal irritations of the

stomach lesion when, owing to hereditary predisposition and other influences, there exist greatly weakened resistence in the subcortical strata of the brain. There frequently exist then concurrently psychic disturbances, which will be gone into later, arising from the same predisposition (vide Strümpel's Psychasthenie), the moving cause of which lies in centripetal irritations of the stomach lesion. Where, therefore, there is heightened excitability, whether psychic or motor, the removal of the cause, in other words, a causal therapy, is unconditionally necessary so long as there is a possibility of removing the cause. All symptomatic therapy is to be rejected for the reason that this, as also medicinal symptomatic therapy, as shown in the foregoing, is generally injurious or because it can at the most only alleviate, just as also the physical or hydrotherapeutic therapy. The latter treatment can, therefore, only be turned to account for the supporting of the dietetic cure so far as it is compatible with the much more important factor of bodily rest. Nowhere are so many errors committed as in the treatment of neurasthenia, owing to the overlooking and entire neglect of the primary disease, and that in consequence of a one-sided specialistic examination which does not embrace all the organs, or in consequence of too hasty examination. The stomach troubles complained of, where such are present, are put down to the neurasthenia, regarded as nervous dyspepsia, a view which I must oppose, as Kussmaul also did. I have observed a great number of patients who were treated for years for so-called neurasthenia, until in the end they became confined to bed, or through the onset of gastralgia, gastric hemorrhage, they became aware of their primary disease, patients whose curing required nothing further than a causal diagnosis and causal treatment. The mere discovery of a cardiac dilatation leads us at once to the correct causal diagnosis, for which reason every examination in cases of neurasthenia should commence with the minute examination of the heart. Here, too, may there set in at least a change in the views held concerning the nature of neurasthenia, for in no other domain has there been so much fruitless treatment, extending over many years, to the injury of the patient, and also to the prejudice of our professional esteem.

Of importance for the dietetic treatment is also the falling off in the attentive faculty, brought on by the action of gastric or gastro-enteric toxins, the difficulty attending the reasoning processes and the observant faculties, the weakness of memory, in general the decrease of the entire mental working powers. As has been shown elsewhere,[27] these disturbances in the cerebral functions are due to the fact that, under the influence of the aforesaid toxins, the chemical composition of the protoplasm of the ganglion cells is changed, and the storing up of mental pictures rendered more difficult and slow. Possibly,

too, analogous to the operations in melancholia, which we have still to discuss, owing to the influence of gastric toxins, the conduction of the associative fibers is rendered more difficult and slow, all of which would explain the difficult working of the observant faculty, and the falling off in the performances of the mental powers. In consequence of the aforementioned alteration in the protoplasm of the ganglion cells caused by the toxins, the molecular compositions of mental pictures are destroyed, or at least the physiological disintegration of these stores is accelerated, thus conditioning the weakness of memory. As has been proved, for these disturbances of the cerebral functions the afterconditions of the gastro-intestinal disease, anemia and malnutrition, in absolute conformity with what was found to give the moving cause to neurasthenia, and to the psychic disturbances still to be discussed are of only entirely secondary importance, as the cerebral functions and their maintenance within fairly wide bounds are, contrary to all expectation, independent of these changes in the blood and state of nutrition. The weakness of memory, the falling off in the performances of the mental powers, may attain such proportions that fears arise in the patients of the oncoming of mental paralysis, and they become entirely useless for their calling.

As a result of the dietetic treatment of the primary disease, even the most severe degrees of memory weakness and decrease of mental working power disappear, so long as the patient has not gone past his sixty-fifth year of age. Beyond this age the memory and mental performances, as the records of observations go to prove, remain defective, in spite of the complete removal of the toxins of the fermentations and decompositions. The presence of syphilis, particularly when accompanied at the same time by chronic alcoholic excesses, must always make us, in advanced stages of this functional disturbance of the brain, very cautious in arriving at our diagnosis, lest we overlook a just commencing dementia paralytica. Not alone, however, does this call for speedy removal, but also in this aspect of the disease, complicated with chronic alcoholism, the speediest possible removal of the fermentation and decomposition processes of the gastro-intestinal canal invariably present in cases of chronic alcoholism is imperative, so that, with the observance of strict abstinence on the part of the patient, degenerative cerebral processes may be prevented. As investigations have shown, the gastro-enteric toxins alone can not constitute the moving cause of such processes. In the case of dementia paralytica, as is well known, the utmost we can achieve is in the direction of an early prophylaxis. A not-too-inferior brain is able to deal with one toxin, but not with a number of poisons operating at the same time. For the normal development of the brain from adolescence to advanced age, for the preservation

of readily acting mental working powers and alertness of intellect, for the conservation of the memory, the entire prophylaxis is founded on the warding-off of gastric and gastro-enteric fermentation and decomposition processes by means of a simple, temperate, and regular manner of life.

Of importance further is the dietary treatment for the removal of sleeplessness, so far, of course, as this represents a disturbance of the cerebral function, and is not caused by pain, etc. This disturbance of the cerebral function is especially fateful for the patient, inasmuch as it deprives the brain of the possibility of resting. Under the influence of want of sleep, neurasthenia and nerve debility assume ever-increasing proportions. As has been shown elsewhere,[28] the causa movens of this sleeplessness is supplied by the toxins of the fermentation processes in the stomach and small intestine. As was shown in the work quoted, this condition is removed by dietary treatment, even in cases where pronounced anatomical cerebral changes are present, so long as these pathological changes do not have their moving cause in pain or other phenomena of irritation disturbing the sleep, as illustrated, for instance, in dementia. In the work in question I directed attention to the serious injuries which here, too, are involved in the symptomatic treatment of sleeplessness by means of soporifics. Investigation and experience warrant me in saying that no method of treatment has done so much damage, and, above all, brought permanent ruin to so many human lives, as the treatment of insomnia with narcotics, exerting their influence as they do in quarters entirely removed from the actual seat of the disease. Instead of removing the cause of the sleeplessness, the toxins circulating in the blood, the measures with which this treatment sets to work are such as injure and even paralyze the functions of the ganglion cells, and which, if their use is continued too long, must inevitably bring about changes in the plasma of the ganglion cells, and even, as is the case with chloral hydrate, symptoms of degeneration. This takes place the more easily that at the same time the influence of the toxins of the fermentation and decomposition processes continues, at the least diminishing the resistance of the ganglion cells. Even if we had at our disposal an ideal soporific, one which could do no damage of this kind in the brain, and which at the same time would not, as do all the opiates with which I am acquainted, accentuate the fermentation processes in the gastrointestinal canal, and more or less severely injure the latter itself, still it is only logical that all we could do would be to suppress a symptom, nature's warning of the presence of serious disorders in the body, while these disorders themselves would work on unimpeded, and could only continue to give rise to grave injuries in the body.

As, however, such an ideal soporific has still to be discovered, the use of drugs in the treatment of insomnia is tantamount to adding to the toxins produced by the fermentations and decompositions other damaging elements, with only an accentuating action on the toxic influence of the latter processes, and this we call a treatment of insomnia. The other methods of treating sleeplessness hitherto practiced, as in the so-called "natural" method of cure, are no better. As in the case of hydro-therapeutics, the utmost they can do is to facilitate the elimination of the toxins, but only after their pernicious influence has been exerted on the body to the full. These considerations imperatively demand of us the causal, particularly the dietetic, treatment of insomnia, for this treatment alone, in the presence of fermentation and decomposition processes in the gastrointestinal tract, can remove, in a certain and lasting manner, this severe disturbance of the cerebral function, and also at the same time bring about the removal of all the other serious disorders of the body existing side by side with sleeplessness, particularly the severe atony of the heart, preventing at the same time the breaking down of strength. Let him who henceforth turns away from these considerations at least be aware of the heavy responsibility which he takes upon himself in continuing the hitherto customary symptomatic treatment of sleeplessness, and let him ask himself whether under such circumstances he can still claim to be considered a counselor of suffering humanity in this grave disorder.

Of the very utmost importance is the dietetic treatment of melancholia, the dependence of which on fermentation and decomposition processes alone has been shown at length elsewhere[29] in the records of 25 years' observations. This is undoubtedly one of the gravest mental disorders, rendering its unhappy victims profoundly wretched, from no cause and for no fault of their own, driving them often enough to suicide. It is a disorder in the presence of which we have hitherto been at our wits' end, but for which now, thanks to this dietetic treatment, a speedy and sure cure is available. In the work in question I have alluded to the well-known case of the spontaneous healing of this mental disorder simply and solely through the diet, which Kant, our famous philosopher, imposed upon himself, thoroughly testing it by exact and long-continued observations in his own case, after all the attempts of physicians to help him had been fruitless. Exactly as in the case of diabetes, the graver forms of toxic albuminuria and phthisis, so also for the genesis of melancholia, the predisposing cause, the diminished power of resistance of the brain, whether due to hereditary influences or to later injuries, is unconditionally necessary. Emphasis is, however, to be laid on the fact that here, too, fortunately, the causa disponens can never be a permanent bar to the healing of the complaint, as soon as

the causa movens, the fermentations and decompositions in the stomach and small intestine, is entirely removed, but can at the most only delay it for a time. The retarding of the association of ideas in this disorder has, in a way, its pathological analogy in the bradycardia present in conditions of exhaustion of the cardiac muscle, with concurrent atony of the latter as equivalent pathological-chemical effect of the fermentation toxins, and it is not uninteresting to find a reminiscence of this disturbance of the cerebral function in the functional disturbances of such an entirely differently constructed organ. The more cases I have seen of melancholia the stronger has become my conviction that for melancholia and its subtypes there is only a single causa movens, the formation of gastro-enteric toxins, and careful investigations made in the large State lunatic asylum at Illenau in Baden, as also the results of the treatment carried out in that institution, have only further strengthened my conviction. I feel that I must at this point express my sincerest thanks to my colleagues on the staff of this institution, and especially to Geheimrat Dr. Schüle, for the obliging courtesy they showed me. The proneness of the fermentation and decomposition processes to relapses, particularly after long duration of the disease, as result of the weakened and often severely injured digestive organs, in association with the very extremely important causa disponens, which always remains unchanged, and which will probably never become susceptible to therapeutic influences, furnishes a complete explanation of the extraordinary proneness to relapses of melancholia. This circumstance renders it incumbent upon us, after we have effected a cure, to urge the patient, with a view to preventing relapses, to diet himself to a certain extent for the rest of his days, and this in a manner in keeping with the tolerance of his digestive organs. But in the case of every sufferer from gastric complaints with slight conditions of depression, we must be concerned, in the interests of the prophylaxis, to effect a cure of his complaint as speedily and certainly as possible, for, from the accounts so frequently given me later, all that had restrained such patients from taking the last step, that of self-destruction, was the confidence inspired in them by the conscientious examination, associated with the most thorough discussion of the case, and the setting in with absolute certainty of a palpable improvement after the long succession of failures. In the whole domain of medicine few situations will present themselves so pregnant with responsibility as those presented by sufferers from gastric disease with conditions of depression, especially when there is a history of suicide in the family with its suggestive influence, or an "idée fixe" prompts to self-destruction, or when unfavorable external conditions, as poverty, lack of employment through constant

past, actually created, or at least decidedly favored, such degenerations, in reciprocal action with the toxical processes supplying the moving cause of the psychosis.

There is no doubt in my own mind that still other hurtful influences, situated outside the brain and operating thence, are of importance as moving cause of psychosis, of which we have such classical instances in the toxic action of strong doses of alcohol, belladonna, toxins of severe infectious diseases, pellagra, the influence of which is varied according to the extraordinarily different individual resistance power of the brain. It is true, indeed, that in order to achieve this ideal of a casual therapy of mental diseases, the education of our alienists must be on altogether different lines. They should be, first and foremost, well schooled in internal diseases before concerning themselves with the difficult subject of psychosis, and furthermore they must thereafter never lose touch with the progress of internal medicines, for only under these conditions can causal therapy make further progress in the field of psychosis, with all its great responsibilities. I regard the hitherto one-sided education of our specialists in nervous and mental diseases as furnishing the chief reason why our therapeutic efforts in this field have as yet made so little advance, being restricted for the most part to the discovery of new sedatives and their activity or satisfied with the advancing of new hypotheses; for this reason, therefore, endeavors in the field of causal therapy have been so fruitless that many doubt, or even deny, that anything is to be hoped for from therapy along such lines. As direct hindrance to the exploration of causal therapy must be regarded also the decree of the Medical Association in Germany, that a physician shall not specialize at one and the same time in two branches, such as that of gastrointestinal diseases and that of nervous disorders. The hitherto customary symptomatic treatment of persons suffering from mental diseases with narcotics, or the whole army of milder sedatives, with its momentary successes and its serious disadvantages—the continuance of the primary disease and even the aggravation of the latter through all these preparations—is open to the gravest suspicion, and has been justified only so long as we, lacking a true insight into the nature and the origin of the mental diseases, could know of nothing better.

In the scheme of treatment of mental diseases in the past, the weighty factor of mental, and generally also bodily, rest alone found a place, whilst the second most important factor, the dietetic treatment, was, at all events in the case of the psychoses under discussion, unfortunately entirely neglected. In view of the great frequency of functional disturbances of the gastrointestinal canal, as also the frequency of its diseases, above all its lesions, which often enough remain entirely latent, and in view of the extraordinarily unfavorable

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f morbus basedowii, forced alimentation is very fre-
practiced in sanatoria, so that I feel compelled to revert
in to this method of treatment. As has been mentioned at
points in the foregoing, the records of careful investigations
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bounds independent of the condition of nutrition and the
of anemia. For this reason alone forced alimentation in the
cerebral functional disturbances can not logically find any
ndation within the confines of a causal therapy. On the
nd, forced alimentation, to be logical, must have as abso-
spensable stipulation a completely intact, or at least not
jured, digestive tract, but particularly the absence of
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gs must of logical necessity lead at once to an ever-increas-
ness and injury of the digestive tract, particularly, how-
severe injuries of the gastroenteric fermentation and
osition processes already so frequently alluded to. If we
strictly with these logical demands of nature, we shall
recognize how extremely seldom are we, unfortunately, at
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recovered from its disease, still in a weakened condition and prone to relapses, an overtasking of its functions, which would at once expose it to the danger of a relapse.

It will be seen from what has been said that after the factor of rest the dietetic treatment is, for a very great number of most important disturbances and diseases, the most influential factor in the cure, and that this treatment, within the bounds of a causal therapy, entirely replaces the palliative treatment by medicaments that has been practiced in the past. The cognizance of the causal connection of manifestations of disease, of disorders, of diseases, with the affections of the digestive tract, simplifies in many respects the clinical classification of diseases, as then many of these disorders fall from their position as independent diseases and have to take their place among the manifestations of disease, and it simplifies also to a very great extent the plan of treatment of these disorders. The recognition of this causal connection explains to us, moreover, the teaching of clinical experience, viz, that the diet is a vastly important factor in the treatment, not only of the diseases of the digestive canal, in which its importance is self-obvious, but also of the diseases of metabolism, the affections of the urinary passage, the disorders and diseases of the central nervous system, the heart and the lungs, in which its importance would not at first sight be suspected. As, however, it falls to the synthetic functions of the digestive canal and the liver to see that all articles of food find their way into the circulation only as matter fit for the use and building up of the body, whereby they lose any possible injurious properties, the therapeutic operations of the diet in disorders and diseases had remained for us hitherto problematical. Through the recognition of the causal connection of all the disorders and diseases mentioned with the affections of the digestive tract, the diet and its vast, far-reaching importance appear to us in an entirely different light. One sees at once without difficulty what crude mistakes have been made in the past in compiling the diet, particularly in the disorders of metabolism, but even also in the disturbances and diseases of the digestive canal, simply because the causal connection of the disorders not being recognized, entirely different causes were assumed, and we set to work groping our way in uncertainty and expose it to the danger of a relapse.

The real causes which demanded a diet, and only a diet adapted to these causes, were entirely overlooked, and many of the articles of food, which we must strictly forbid wherever these causes are operative, were actually regarded as possessing dietetic value. More than this, the diet, in the entire absence of any settled foundation, experienced the most varied interpretation, according to the standpoint which the therapeutist took. Often enough did it go astray

along entirely wrong paths, to instance only the vegetarian diet for constipation, the ordering of fats in diabetes, increasing the danger of coma diabeticum, and instead of bringing the intended benefit its action was directly prejudicial. Thanks to the investigations made in causal diagnosis and in causal therapy, there has now been laid out for the diet, in its nature and composition, well-defined bounds, and it is now, at all events as far as a great number of the most important and gravest disorders of the body are concerned, firmly established. I am by no means blind to the fact that for the time being the standpoint I take is entirely exceptional, and one which to many may even appear revolutionary. But we must at length do away altogether with the old routine of palliative treatment, which is good for nothing but to prescribe a remedy for every disorder, never asking whence the disorder originates, to what primary malady it owes its moving cause, and, above all, what further injuries for the body are involved in the overlooking of this primary disease. This palliative method of treatment is unfortunately so entirely in keeping with the present-day trend of thought, our easy-going superficiality, our overhurried methods of examination and diagnosis, and will prove a deeply rooted evil which will only very slowly be extirpated. It has, however, rendered our position toward suffering humanity almost untenable, has debased many a therapeutist to the position of chemist's hodman, and has not infrequently lent countenance to offensive advertising practices on the part of chemical manufactories and quacks. Above all things, however, the symptomatic therapy which has obtained till this day has been an obstacle in the way of the vastly important investigation of the laws of nature, so far as they have sway in the field of pathology.

We must seek for pathology exactly those same foundations, built up only on the laws of nature, which have proved such a blessing to physiology, in the absence of which sure-going clinical research is a sheer impossibility. Let us, therefore, when and wherever it is possible for us, forsake the path of this faulty palliative treatment and set our faces steadfastly toward a causal therapy, built up on the sure foundation of a most thorough examination of every organ. A causal therapy, and this alone, enables us to be conscientious advisers of suffering humanity, advisers whose counsel is never fraught with detriment to the sufferer, and to be at hand with prompt, lasting, and certain help within the utmost bounds of human power. It relieves us entirely from the moral responsibility for the failure of our treatment, in the absence of the strictest obedience on the part of our patients, or in consequence of incurable conditions, and with its rapid and assured successes vouchsafes an inward satisfaction amidst the stress of our difficult and responsible calling. These suc-

cesses of the causal therapy, however, must in their turn spur us on to further research, to further investigation of the causes of disease, and of the causal connection, based on natural laws, of pathological phenomena, and thus to a more and more perfect building up of the structure of our science. Along this path of research we may hope to achieve results which shall hold good for all time, no less than will the laws of nature, on which they are and must be grounded.

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[2] Die Beziehungen der Magenkrankheiten zu den Erkrankungen und Funktionsstörungen des Darmkanals. (Plönies) (Archiv für Verdauungskrankheiten, vol. 12, No. 2).

[3] "Die diätetische und medikamentöse Behandlung der von Magenerkrankungen abhängigen zerebralen Funktionsstörungen und Psychosen." (Plönies), (Archiv für Psychiatr., vol. 48, No. 2).

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THE HYGIENIC PHYSIOLOGY OF BATHING AND ITS APPLICATION TO PUBLIC BATHS.

SIMON BARUCH, M. D., Professor of Hydrotherapy, College of Physicians and Surgeons, Columbia University, New York. Consultant to Bellevue, Hood Wright, and Montefeore Hospitals.

The hygienic physiology of baths has changed with the changes in the conception of the physiology of the skin. When I studied medicine 50 years ago, elimination was regarded as the chief function of the skin. The textbooks related the story of a boy who, after being covered with gold foil, had represented an angel in a papal procession, and who died because the impurities which it was the function of the skin to eliminate were retained. I must confess that not long ago I risked being regarded as uninformed on modern physiology when I argued before an aldermanic committee for new public cleansing baths that the skin purifies the organism just as do the lungs, and that therefore free cleansing baths are as important to the community as free parks. Our present knowledge of the physiology of the skin makes its eliminating function the least important in hygiene for the maintenance of life under normal conditions. In this presence it were an act of supererogation to dwell upon the following facts, which are indisputable, were it not probable that the discussion of this section may be utilized for the diffusion of physiological knowledge of the bath among the lay people. It is an indisputable fact that to the nerve and vascular supply ramifying in its structure the skin owes its life-sustaining functions, and that these underlie the sense of

touch which is the most vital of all the senses, because its extinction is fatal, while every other sense may be destroyed without actual loss of life. It is now positively known that death of animals which have been covered with an impermeable varnish, as was the gilded boy, is not due to interference with the purifying function of the skin but to interference with temperature regulation, and that if the temperature is maintained by enveloping the animal with warm coverings it may survive for some time. There is a sudden rise of temperature after varnishing the animal, it becomes weary, the pulse and respiration become rapid as in fevers, albuminuria and convulsions ensue, exhalation of CO_2 is reduced enormously, and finally the animal expires with a temperature far below the normal.

While elimination is secondary to temperature regulation, it does play an important rôle in the physiology of the skin. Since it is the function of hygiene not only to maintain health but to fortify the system against disease, it is relevant and indeed necessary to advert here to the fact that in health the skin excretes an almost negligible quantity of CO_2 in moderate temperatures (−29° to 33° C.), but that the quantity is doubled when 34° C. is reached, the watery secretion increasing pari passu, probably by reason of enhancement of glandular activities. Only in diseased conditions, in which all the compensating activities of the organism are called upon to maintain life, the full excretory capacity of the skin comes into play. In asthma and certain heart affections in which the respiration is embarrassed to the point of danger a marked increase of aqueous vapor and CO_2 has been noted. Thus is the patient tided over impending suffocation. Precisely the same compensatory activity is found in the enormous excretion of urea in kidney failure, while the largest quantity of urea recorded in health is 2 per cent of the perspiration; the quantity is enormously increased in cholera, Unna and others having reported that the deposit of urea crystals may be scraped off in large quantities. Cases are also reported in the literature of clinical medicine, in which various pathogenic organisms have been found in miliary vesicles and in the perspiration, streptococcus albus and aureus and diplococci. The maintenance of the integrity of this function becomes a matter of paramount importance, therefore, when diseases attack the body, in which resisting capacity is the chief protecting asset to meet the impending dangers.

What is the physiological action of the bath? We are confronted with a very large subject which I must treat briefly on account of the pressure of time. Bathing may be defined as the act of applying water to the skin. The activities aroused in the latter are due to the thermic and mechanical excitation of the nerve terminals and vessels ramifying through the cutaneous area which are subjected to this excitation. Prolonged observation has convinced me that some of

the commonly accepted explanations of the action of cold water and hot water upon the skin are erroneous. Cold water has been hitherto regarded as conveying to the skin vessels and nerves a decided irritation which is transmitted on sensory tracts to the central nervous system and thence reflected on motor tracts to the various organs, chiefly those of respiration and circulation, and through the latter upon secretion, excretion, and tissue change. These effects have been termed reaction. I am entirely in accord with this view so far as it applies to very brief applications of cold water.

For example, when a healthy individual takes a cold shower, say of a temperature of 15° or 20° C., of brief duration, this rationale suffices; it also would explain the action of a plunge of the shortest possible duration into water at that or a lower temperature. But when the exposure to the cold water is prolonged for several minutes, this process, which I have termed "nerve reaction," is supplemented by what I have termed the vascular reaction which is not general, but local, i. e., the thermic excitation is exerted upon the ganglia controlling the local peripheral vessels and the unstriped muscular fibers which form a network or web with the elastic fibers, and together constitute, according to Unna, the oblique tensors of the skin, and which together with the arrectores pilorum control the blood supply of the skin, according to Tomsa and Sappey. That the cutaneous muscles are subject to contraction by cold and relaxation by warmth is plainly demonstrated in the dartos and by the familiar cutis anserina. The enormous capillary area ramifying in the papillary spaces being an aggregation of epithelial tubes without riphery, where it meets resistance which enhances the ventricular contracted muscular web surrounding it. The blood is driven from this superficial area which remains partly empty (it becomes entirely empty under low temperatures) so long as the cold water surrounds the skin. The vasomotor stimulation aroused by the thermic excitation primarily induced having aroused the heart to increased activity, the latter drives the blood with greater force toward the periphery, where it meets resistance which enhances the centricular contraction, thus establishing a salutary circle. When the individual emerges from the bath, the warm blood received in the capillaries dilates the latter and removes the contracted state of the muscular fibers surrounding them. This frees the capillaries, which by their normal resiliency are now enabled to dilate and under the increased ventricular action are filled beyond their normal caliber. The skin assumes a ruddy hue, all the functions are stimulated, and there is a general refreshment and invigoration. Thus tonic reaction ensues. That this theory is not without legitimate basis has been demonstrated by an experiment made upon himself by Dr. Heinrich Wolf, of New York, in the physiological laboratory of the College of Physicians and

Surgeons, Columbia University, under observation of Prof. Burton-Opitz. A plethysmograph was filled with water at 46° C. after the right arm had been inserted. Nitrate of amyl was then inhaled until distinct throbbing was felt in the head. The volume of the arm increased decidedly. The plethysmograph was then filled with water at 30° and nitrate of amyl inhaled until its physiological action was noted; the volume of arm diminished, although the characteristic pulsations in the head increased, showing that the dilation of the arterioles of the skin was counteracted by the effect of cold on the muscles enmeshing the capillaries.

This rationale of the action of cold water in the production of tonic reaction which is the most important element of the hygiene of the cold bath reconciles the views of two opposing factions—one represented by Wilhelm Winternitz of Vienna, who has held tenaciously for a long time the view that the muscular walls of the arteries and arterioles of the skin are contracted by cold baths, and that after the removal from the latter this contraction is released with filling of these vessels to repletion by reason of the enhanced vasomotor action. This idea remained undisputed until Mathes pointed out that when a muscular structure contracts it is a tonic process, but when it dilates, as Winternitz claimed, it was passing through an atonic process. Nitrate of amyl, for instance, produces a dilation of the outlying arteries and arterioles which is atonic in character. My explanation reconciles these opposing views, since it disposes of the error that the arteries, or even the arterioles, are contracted in the ordinary of the cold bath. Only the most intense and persistent cold, like that produced by ice or ethyl chloride, is capable of reaching the deeper lying vessels, and when they are emptied the skin becomes pallid, and if continued long the skin dies. A brief and readily tolerated application of the cold bath never produces this manifestation; in fact, reaction is initiated before the individual emerges from the bath. The warm bath, on the other hand, relaxes the cutaneous muscular structures, permitting a dilation of the capillaries arising from the thermic mild stimulation induced. The latter ceases very soon, there is no resistance at the periphery, the increased vascular area in the skin causes diminution in the internal blood supply; this condition of the cerebral capillaries sometimes giving rise to fainting. There is a hydrostatic action also, as ascertained by Schuller in his experiments in trephined rabbits and confirmed by Vinaj in a trephined man, showing that when the cutaneous vessels are contracted the cerebral vessels are dilated, and vice versa. We have therefore a general reaction supplemented in prolonged procedures by the vascular reaction in the skin, which reacts upon the general circulation.

Another remarkable effect of the bath is that cold water increases the number of red and white blood cells taken from the lobe of the ear before and after the bath, while warm water increases the white cells chiefly. This change in the number of blood cells after the bath is due to the fluxion produced by more vigorous cardiac action, which drives these cells from places where they are sluggishly floating into the general current, thus adding to the invigorating action that exposure of a larger number of white cells to oxygenation. Hæmoglobin is increased 10 to 20 per cent after cold baths, and not at all, or reduced after warm baths.

The influence of baths on the respiratory processes is pronounced. The scapular and epigastric reflex areas of Head being connected with the first seven dorsal ganglia and the vasomotor supply of the lungs also passing through the roots of these gangliæ, there is doubtless a direct connection between the skin of the upper part of the trunk and the circulation of the lungs, from which arise alterations in the caliber of these vessels when the cutaneous nerves are stimulated or depressed by cold or hot water during a bath.

It is not surprising, therefore, that Rubner reports that short baths at low temperatures evoke decided changes in the respiratory processes, as follows:

Bath.	Volume of air.	CO_2.	O.
At 16°	+22.9	+ 64.8	+ 46.8
At 30°	+ 7.3	+ 31.0	+ 16.2
At 33°	+ 1.8	− 6.8	+ 6.2
At 40°	+16.1	+ 3.9	+ 3.2
At 44°	+18.8	+ 32.1	+ 17.3
And a douche of 16° C	+54.5	+149.4	+110.1

This effect disappeared in an hour, but would certainly be enhanced by exercise. It may be noted that when the normal temperature of the skin is approximated by the bath temperature the reaction is at its minimum. For a long time I have observed this fact, and several years ago I formulated a law to this effect. The intensity of water applications to the skin is governed chiefly by the difference of temperature between the water and the skin. The normal temperature of the skin after removal of clothing ranges between 33° and 34° C. Rubner's experiments confirm many which I have made. showing that the greater the deviation of temperature of the water from that of the skin the more intense is the primary stimulation of the bath—and this holds good whether the temperature goes up or down. In a lecture before teachers of the medical schools, in Philadelphia, published in the International Clinic, Prof. Tyson asked why it would not be better, according to my law, to give the preference to warm water, which is more agreeable than cold water. The answer is

Physical therapy, however, remained absolutely neglected, this being especially the case with hydrotherapy. This was left in the great majority of cases to the laity. The merit of having laid the definite foundations belongs incontestably to Wilhelm Winternitz, since he, chiefly through his own experiments, brought the laws of physiology on thermal and mechanical stimulus into relation with hydriatic procedure. Winternitz's pupils, and especially Dr. S. Baruch (New York) and other investigators, working in the now so flourishing field of physical therapy, have built up and extended the doctrine of hydrotherapy by their researches. Water treatment can not remove the causes of anatomical disease, and hydrotherapy must therefore be placed on the same footing as other methods of treatment, such as are used for again stimulating the functions of the organs, or in favorable cases, of reestablishing them. The skin serves as the means of contact, or more rarely the externally accessible cavities of the body. In some cases water is internally incorporated with the body through the mouth and stomach in a strictly prescribed and methodic manner. Water, for healing purposes, when applied exteriorally is used in fluid form, or as steam, or ice. Experience in water treatment is then of service as regards the stimulus, which water of different temperatures calls forth, and also as regards the mechanical stimulus effected by the height of fall or pressure when working upon the body, as well as by a rubbing, kneading motion, carried out on the patient externally, while sitting in the water. All these measures are exactly calculated and apportioned by doses. Hydrotherapy, then, consists in the art of measuring thermal and mechanical stimulus so exactly, as to produce a soothing or stimulating effect, according to desire. This stimulus, then, can be directed in fine nuances over the whole body or over definite portions only.

Every skillfully carried out procedure by water must arouse a feeling of comfort in the patient. Under no circumstances must he be allowed to take a chill afterwards, but on the contrary a pleasant feeling of warmth must course through his veins. This so-called reaction, that is, the rewarming, gives us a guaranty in all cases of properly conducted treatment by water. This ought to increase the richness of the blood of the skin and thereby remove inflamed and overloading matter from the internal organs. Skillful alternation of cold and warmth stimulates the skin and buttock muscles in a gymnastic sort of way, and is then the better able to withstand external influences. The activity of the skin is hereby improved and enabled—partly at least—to substitute those extremly delicate secretive organs, the kidneys, and consequently to remove substances from the body, which if left therein, would lead to poisoning and death. The acceleration of the circulation and respiration after application of water

conducts more air and thereby more oxygen to the interior of the body, and at the same time, improves powers of digestion and the whole condition as regards nutrition.

In consequence of the lowering of a threatened rise in temperature; of the strengthening of the natural weapons of protection and resistance, direct and reflex; of the favorable influencing of the nervous system, as well as of the heart, cure by water treatment has already for ages been extensively used successfully in fighting all infectious diseases, as well as in the so-called children's diseases, measles, scarlatina, etc.

Hydrotherapy makes use of water in the form of hot or cold full baths, hip baths, and wet packs, which act in a more soothing manner; while rubbings, shower baths, ascending douches, cold-plunge baths—of others—serve to stimulate. The great host of wet partial compresses, local douches, affusion, cooling apparatus, etc., completes the equipment of cure-by-water treatment. Other branches of physical therapy, such as electricity, massage, curative gymnastics, and light therapy are also made use of, as required, in connection with the use of water.

Hydrotherapy is now proving itself, in practice, serviceable and of benefit in all branches of medicine, in surgery, in gynecology, in dermatology, in treatment of the ears and eyes, and above all in internal medicine.

It would naturally be quite impossible within the limits of this paper to more than touch upon the clinic of hydrotherapy to quite a slight extent, and I shall therefore confine myself to briefly picking out at random some groups of diseases, to show that therapeutic treatment of hydrotherapy acts entirely in accordance with biological laws.

The fine gradations and adjustments of treatment by water enable hydrotherapy to become an excellent means of fighting against disturbances in the activity of the brain and spinal marrow, just according as they are met with as overstimulus or laxness. Hydrotherapy invests us with the power of allaying pain, inducing sleep, and in addition thereto, possesses a means of rousing patients out of a state of lethargy, as well as of freeing them from gloomy reflections. Hydrotherapy is valuable therefore as a suitable field of operation for those suffering from neurasthenia and neurosis; some cases of phsychosis, such as melancholia and mania, are also favorably influenced by certain hydrotherapeutic measures.

It would be going far outside the limits of a paper like this were I to go into all the particulars of the hydriatic treatment of organic diseases of the nerves, as my institute in fulfilling its object has to do, so I will therefore confine myself to quite a brief survey of the hydriatic treatment of tabes dorsalis, the most frequent of all spinal

diseases. Here the first thing of importance is to lower the tendency to excitement and pain.

The capability of reaction of the tabes sufferer must ever be kept strictly under observation and the intensity and duration of the process be guided thereby.

In addition to full baths, hip baths of from 34° to 30° C. without friction, but with gentle affusion are used (Winternitz). As a remedial tonic, in accordance with Hösslins's directions, I let this be followed by a short cold stimulus in the form of ablution or slapping of the nether extremities, this lasting only 6 or 8 seconds, and being carried out while sitting. Hydrotherapy possesses in hip baths of from 34°–37° C. and of long duration, in stimulating compresses or steam bottles—the stomach remedy of Winternitz—and so forth, remedial aids against painful crises and the lancinating pains of tabes, sufficient to often help the afflicted one over his martyrdom.

We have also seen the troublesome and disturbing symptoms of complex sclerosis improve under the influence of the hip-bath treatment above mentioned. I have already pointed out the superiority of physical therapy, and especially of hydrotherapy, over all other methods of treatment in neuralgia, and particularly so in that of the sciatic nerve.

Superficial neuralgia is favorably acted upon by electric rays, or in conjunction with a complete rubbing; while persons who, in spite of all medications, injections and baths, medicines, electrizing, etc., still suffer from such severe sciatica that they are almost bent double, can be again restored by my special form of motion baths. We will let this fragmentary survey of hydriatic treatment in nervous diseases suffice. I should not like it, however, to be supposed that I by any means consider hydrotherapy to be a universal panacea for all ills, but I do say that, as a symptomatic remedy, the exact methods of healing by water with its so simple and in all its external relations so adaptable a technique, should alone, or, according to circumstances, also in conjunction with our other means of treatment, have more attention paid to it in medical practice than has hitherto been the case. I will here only just touch upon some groups of disease, so as not to take up your time too much.

The treatment of diseases of the muscles of the joints by means of hydrotherapy is one, however, that will well repay attention. We use for this an application of hot fomentation, special preference being given the combination of the steam douche with massage and bodily movements—the so-called steam-douche massage. The diseases of the joints, which are most clearly indicated for steam-douche massage, are those arising from rheumatism, gout, and especially from gonorrhea—particularly of the monoarticulate form. The most noteworthy

DISCUSSION.

Dr. J. H. KELLOGG: Water is the oldest and most valuable of all remedial measures. It was largely employed by the ancient Egyptians and is habitually used by the savage tribes and by wild animals. A hundred years ago the eyes of the whole world were turned toward Graefenberg, a mountain village in Austrian Silesia, by the marvelous cures effected by Priessnitz, a peasant doctor, by the use of water. Many eminent physicians followed the thousands of sick people, who flocked to Graefenberg from all over the civilized world, for the purpose of studying the methods used and learning the secret of the success of the illiterate empyric whose fame as a healer had extended throughout the world.

About 50 years ago Winternitz, of Vienna, visited Graefenberg and began the study of hydriatic processes, a study which laid the foundation of scientific hydrotherapy. Nearly 40 years ago Dr. Baruch, of New York, began writing papers on the subject in this country. His physiologic and clinical researches entitled him to be called the Winternitz of America.

Prof. Dr. Brieger has been for many years doing in Berlin the same work which Winternitz has done in Vienna, and through his efforts the teaching of rational hydrotherapy has been introduced into the curricula of all the leading German universities.

Dr. Baruch rendered a public service of the highest importance in establishing in New York years ago the first public baths in this country, an example which has been followed in many of our leading cities. The movement is rapidly extending and it is to be hoped will continue until not only every city but every public school shall be provided with douche and swimming baths.

The able papers of Drs. Baruch and Brieger presented this morning set forth physiologic facts and principles of inestimable importance in prophylactics and therapeutics. The neuro-vascular training effected by the cold bath mentioned by Dr. Baruch is, next to diet, the most efficient of all known means of favorably influencing nutrition and the most potent measure which can be applied for building up the resistance of the tissues.

By proper hydriatic applications it is not only possible to increase leucocytosis and general vital resistance, but to control the blood supply and the function of every organ of the body. By a score of hydriatic methods pain may be relieved; a multitude of different applications induce sleep, encourage elimination, increase or decrease metabolic activity, and raise or lower blood pressure. No other remedy known to man possesses half the versatility and range of application which the hundred or more classical hydriatic procedures permit in the hands of an expert.

practice therein, since hydrotherapy can only be of use in the hands of a medical man well versed in it.

The necessity, therefore, of molding hydrotherapy to the service of the doctor in his practice is making itself felt ever more and more. When I took over the institute of the university on the premises of the Charité in Berlin in 1901 I had much opposition to overcome, especially from doctors. Just about the same thing happened during the earlier development of bacteriology, when the greatest and bitterest opposition came from the highest authorities. My institute now has, out of pure necessity, been extensively enlarged.

The Virchow Hospital of Berlin has fitted up a hydrotherapeutic institute under the conduct of Laquer, who was my assistant for many years. Here is proof that hydrotherapy has gained more adherents in spite of all opposition, and we see new institutes arising in increasing numbers, Zurich University amongst them, at the head of which is my former pupil, Prof. Sommer. The whole of the Prussian University clinics and the majority of other German universities, sanatoria, balneotherapeutic, and watering places are zealously vying with each other in establishing hydrotherapeutic establishments.

The central commission for all the sick clubs of Berlin and suburbs, with 1,000,000 members, decided to fit up an institute similar to the Hydrotherapeutic Institute of the Berlin University, under its President Simanowski, for hydrotherapeutic and physical treatment of its members. This institute also is under my direction and is, on an average, visited by more than 200 club members daily. In France, too, they are beginning to found self-supporting hydrotherapeutic institutes, in pattern similar to mine, in the Hotel Dieu and elsewhere.

The German Army has also some hydrotherapeutic institutes, the best of which is the so-called Officers' Home, at Falkenstein, Am Taunus, under the direction of a former assistant of mine, Oberstabsarzt Dr. Krebs.

Gentlemen, no further statements are surely needed to prove the necessity of treatment by water.

These facts prove conclusively that a wider space for medical training in hydrotherapy must be made, since it is no longer the rich only who are treated in specialists' homes, but the special institutes of the sick clubs, now being fitted up everywhere, prove above all things the necessity of a knowledge of hydrotherapy by the doctor.

Too long has this important branch been neglected and left to cure muddlers, to the injury of mankind and of the doctor. This, however, has now been changed, and must remain so, to the welfare of mankind and to the advantage of the doctor.

THURSDAY MORNING, SEPTEMBER 26, 1912.

COST AND NUTRITIVE VALUE OF FOODS.

Dr. C. F. LANGWORTHY, Chief of Nutrition Investigations, United States Department of Agriculture, Washington, D. C.

In the United States, work which has to do with the nutritive and economic value of food has been actively carried on for many years under a variety of auspices including, among others, the National Government, State and municipal authorities, universities, and agricultural and other colleges, agricultural experiment stations, public institutions, and private and endowed institutions and laboratories. In the five years since the Fourteenth International Congress on Hygiene and Demography was held, the product has been large and varied. With the view of giving an idea of its character and scope, a survey has been made of such nutrition work as has to do with the composition of food as determined by proximate analysis, and by more detailed analyses, as affected by conditions of production, handling, storage, and manipulation; and with nutritive value as related to ease and thoroughness of digestion, the utilization of nutrients and energy in the body, and related topics. Some special studies have also been included, and an attempt is made to gather together at least the more extended of the numerous studies reported of the cost of food and other economic studies.

Like any such collection of data, this summary is necessarily selective, rather than complete, and references are for the most part brief and designed to show where work may be found and its nature, rather than its details and conclusions. Much work which might have been cited is not referred to at all or only briefly mentioned as, without doubt, it will be presented to the Congress at some one of its sessions by investigators who have carried it on.

STUDIES OF FOOD AND FOOD PRODUCTS.

Many studies have been made of the proximate composition of food products, and of the effect upon the nutritive value and quality, of methods of cultivation, of manufacture by various processes, and of handling. As a part of national and State inspection under pure-food laws, hundreds of more or less complete proximate analyses have been made also.

mercial value of different varieties of wheat has been
luding analyses and milling and baking tests under many
variations in composition and quality in different locali-
ularly with reference to the effect of the climatic condi-
varieties, cultural methods, and so on. Such work has
by E. F. Ladd and Emily E. May,[1] also by L. M. Thomas,
North Dakota Experiment Station. Similar tests have been
E. F. Ladd and C. H. Bailey,[2] by R. W. Thatcher,[3] by
Waldron,[4] with California wheats by G. W. Shaw and A. J.
itz,[5] and with a variety of wheats by F. D. Gardner.[6] The
wheat supply of the United States is discussed by M. A.
leton,[7] on the basis of statistical data. Data on the effect of
tic conditions on the composition of durum wheat are discussed
J. A. Le Clerc.[8]

Tempering durum wheat by moistening to improve its milling qualities was found practicable by E. F. Ladd and Alma K. Johnson.[9]

Results of milling and baking tests with spelt made by E. F. Ladd and Alma K. Johnson[10] are favorable to its use for human food.

G. A. Olson[11] studied the effects of soaking and germination of wheat on the distribution and yield of milling products, quality of flour, and bread-making properties. Analyses of domestic and foreign diabetic products in comparison with wheat flour are presented by D. W. Fetterolf.[12] An experimental study of the starch grain was made by H. Kraemer.[13] He concludes that the grain consists of colloidal and crystalloidal substances, for the most part, arranged in separate and distinct lamellæ. In the alternate lamellæ the colloidal substance predominates, associated with crystalloidal cellulose; in the other layers, the crystalloidal substance, consisting chiefly of granulose, occurs in greater proportion.

The influence of a number of chemical substances and milling by-products, as well as germination of wheat, on the baking qualities of flour, were studied by J. T. Willard and C. O. Swanson.[14]

Experiments with salt-rising bread in comparison with bread made from yeast were made by H. A. Kohman.[15]

The composition of a sample of alfalfa bread made from a mixture of dried ground alfalfa and flour which has had much popular notice is given by J. P. Street,[16] as follows: Water 20.48 per cent, protein 10.62 per cent, fat 1.32 per cent, nitrogen-free extract 63.98 per cent, crude fiber 0.95 per cent, and ash 2.65 per cent.

R. O. Baird and C. K. Francis[17] have studied the chemical composition of Kafir corn in comparison with Indian corn, particularly with reference to proximate composition, the composition of the nitrogen-free extract, the character of the fat and ash constituents, and other properties. According to their summary, proximate analy-

sis shows that Kafir corn compares favorably with Indian corn, and they conclude that it is a cheap foodstuff.

Many studies of cane sugar, beet sugar, maple sugar, and honey have been reported.

C. A. Browne, jr., and R. E. Blouin[18] have made an exhaustive study of the parts of the sugar cane and of the plant ash. G. W. Shaw[19] found no considerable difference for canning and preserving under commercial and household conditions between beet and cane sugar.

Maple sap, sirup, and sugar have been studied by H. A. Edson,[20] A. H. Bryan,[21] and A. P. Sy.[22]

Analyses of American honeys are presented by C. A. Browne,[23] and a microscopical study of honey pollen by W. J. Young.[24]

A number of studies of meat, eggs, cheese, and other animal foods have appeared.

P. F. Trowbridge and C. K. Francis[25] have studied the glycogen content of beef flesh and methods of estimating it. From their results, they believe it possible that the older the animal the greater the tendency to store glycogen, all animals 3 years old or over showing more than 1 per cent in the liver. The percentage of glycogen of beef muscle varied from 0.1 per cent to 0.7 per cent, and of beef liver from 0.2 per cent to 3.8 per cent, respectively.

Market classes and grades of meat have been studied by L. D. Hall.[26] Similar work has been published by P. F. Trowbridge.[27] Nitrates in animal and vegetable foods have been studied by W. D. Richardson.[28] Analyses of beef extracts and yeast are reported by F. C. Cook,[29] J. P. Street,[30] and others.

Digestion experiments on the utilization of the proteins of extractive-free meat powder and the origin of the fecal nitrogen are summarized by L. B. Mendel and M. S. Fine,[31] thus:

> The utilization of the nitrogen of meat powder is distinctly, although slightly, lower than that of fresh meat. The relatively high nitrogen concentration of the meat-powder feces is indicative of a loss of this material through the excrement.

The sea mussel was found to be a valuable food by I. A. Field.[32] Dogfish, sand shark, toadfish, etc., were also studied as food by I. A. Field.[33]

On the basis of experimental work, copper was considered to be a normal constituent of American oysters by J. T. Willard.[34]

Bacteriological and chemical studies of eggs are reported by Mary E. Pennington,[35] and chemical analyses of eggs are reported by J. T. Willard and R. H. Shaw.[36] In addition to the usual determinations, Willard and Shaw[37] report phosphoric acid in the yolk (average 1.43 per cent) and ash in the yolk (average 1.57 per cent), and the ratio

of these two constituents 1:1.09. The average thickness of the shells was found to be 0.0139 inch.

Changes in the composition of Cheddar cheese were studied by L. L. Van Slyke and A. W. Bosworth,[38] and chemical studies of Camembert cheese are reported by A. W. Bosworth.[39]

A brine-soluble compound, always associated with calcium, was found in ripening Cheddar cheese by L. L. Van Slyke and A. W. Bosworth.[40]

Small white specks in Roquefort cheese were found to be tyrosin, and not calcium soaps of fatty acids, by A. W. Dox.[41]

The manufacture of buttermilk is described by J. L. Sammis,[42] and of "whey butter" by C. F. Doane.[43]

G. A. Olson[44] finds a new proteid in milk, cream, and butter.

The cultivation, transportation, and shipment of fruits and nuts have been studied more than their composition, food value, and use. Cactus fruits, or "tuna," were studied by R. F. Hare and D. Griffiths;[45] Italian lemons by E. M. Chace;[46] and various fruits and nuts by W. R. Lazenby.[47] Lazenby[48] reports less than 80 per cent water in undeveloped strawberries, peaches, and apples as compared with 90 per cent in fine but not overgrown specimens; and 92 per cent water in fine, large peaches in comparison with 84 per cent in small peaches of the same variety. Grapes were studied by W. B. Alwood[49] et al., particularly with reference to the occurrence of sucrose and variations in the sugar and acid content during ripening in Catawba grapes. The sugar more than doubled after the berries began to color, while the acid was only about half as great. Similar data are reported for many other varieties. Pineapples were studied by W. P. Kelley.[50] Considerable range was found, but on the whole Hawaiian pineapples showed the same average composition as others. Green pineapples, Kelley concludes, contained less acid than the ripe fruit and also a small percentage of fiber, reducing sugar, and sucrose. Dextrine and starch did not occur in important quantities at any stage. The reducing sugars and sucrose stand in an inverse ratio in the green and the ripe fruit.

L. H. Merrill[51] gives analyses of tropical fruits and vegetables, and reports digestion experiments with hulled corn. Popping corn, his experiments showed, affected its composition only by reducing the amount of water.

Much work has been done in the study of enzyms of fruits. To cite a recent example, H. P. Bassett and F. Thompson[52] found an oxidase in green and ripe apples, pears, and walnut hulls, which produced a tanninlike substance in injured fruit and in fruit removed from the tree. This substance is believed to have fungicidal properties. A catalase precipitable by calcium carbonate was also found.

Bread, milk, vegetables, bananas, and rhubarb were included by H. Ackroyd [53] in his study of the occurrence of allantoin in food. Small quantities were found in all these foods.

The value and use of nuts are discussed by M. E. Jaffa.[54]

At the University of Tennessee, Wait [55] studied the composition, digestibility, and nutritive value of white navy beans, red kidney beans, and several varieties of cowpeas. Generally speaking, the legumes were as well assimilated and digested as are the coarser cereal products. The investigation, as a whole, demonstrates the importance of legumes in the diet as economical and palatable sources of protein.

An extended series of studies carried on in connection with the nutrition investigations of the Office of Experiment Stations have had to do with the nutritive and economic value and digestibility of Cheddar cheese made with different amounts of rennet and ripened for varying lengths of time, and with cheese of other sorts. The results have shown that, judged by digestibility and wholesomeness, as well as by composition, cheese is a particularly wholesome, nutritious, and economic food. Summaries of this work have been publish, for instance, The Digestibility of Cheese, by C. F. Doane,[56] but the experimental data await publication in detail.

More attention has been given to the care and marketing of vegetables than to their composition and nutritive value. Some work may, however, be mentioned. Canned and soaked peas and beans of different grades were analyzed by W. L. Dubois,[57] with reference to canning such vegetables and the effect of age upon chemical nature of the legumes and their quality when canned. The crude fiber and the crude starch content of the beans canned before soaking was higher than in the case of the beans canned fresh. As peas mature the ash and crude fiber decrease and the starch increases. Data for ether extract and nitrogen are less conclusive.

Minnie Reed [58] reports studies of edible marine algæ, and gives much data as to their use by native Hawaiians.

Data on insoluble carbohydrates, particularly of marine algæ, and a summary of digestion experiments with such foods in comparison with raw Italian chestnuts are reported by L. B. Mendel.[59]

Carbohydrates of lichens, algæ, particularly marine algæ, and related substances were studied with regard to their character and nutritive value by Mary D. Swartz,[60] who found that the water-soluble hemicelluloses, which are the characteristic constituents of the carbohydrates, are digested little, if at all, by man.

Potatoes and other root crops as food are discussed by C. F. Langworthy.[61]

Proprietary foods have not received the attention which their use, especially in infant and individual dietetics, would seem to warrant.

Lusk [62] deals with the nutritive value of such foods. The same subject is treated by D. L. Edsall,[63] J. Howland,[64] and also in a paper without signature.[65] The composition, especially fat content, of malted milk is reported by G. F. Richmond and W. E. Musgrave.[66]

The breeding of cereal crops, the influence of fertilizers on composition, and related questions have received much attention, especially from experiment station investigators. Though this work is perhaps more closely related to agricultural chemistry than to nutrition, some of the work, especially with wheat and corn, may be considered here.

Wide variations have been reported in the composition of light and heavy kernels of wheat of the same variety, in grain from well developed and imperfectly developed ears of corn, and in the kernels from different parts of the ear.

With reference to work with Indian corn, A. M. Soule and P. O. Vanatter [67] found that many of the best yielding ears had a smaller protein content than the undesirable ones.

C. L. Penny [68] found the protein content in different crops to vary from 6.25 to 12.69 per cent, and the small kernels at the end of the ear to contain on the average 0.3 per cent less protein than the large, well-formed kernels.

In experiments on breeding of corn, L. H. Smith [69] found it possible in 10 generations to increase the protein content from 10.92 to 14.26 per cent or to reduce it from 10.92 to 8,64 per cent. The oil content could be varied by as much as 4.71 per cent.

Data relating to the nutritive value and use of corn as food are discussed by C. D. Woods,[70] digestion experiments and other work being summarized.

Rice has been studied with especial reference to nutritive value and also to the etiology of beriberi, particularly in the Philippines. Alice R. Thompson,[71] who studied varieties in Hawaii, found no greater nutritive value in Japanese rice than in Hawaiian rice. Unpolished rice was found to contain four times as much fat as the polished, also more protein, crude fiber, and ash. All the nitrogen was found to be proteid nitrogen. H. Aron and F. Hocson [72] found that relatively more phosphorous than nitrogen was lost in polishing rice and gave as their opinion that an exclusive rice diet is deficient in protein. V. G. Heiser [73] summarizes practical experience with unpolished rice in relation to beriberi.

The use of cottonseed products as food for man has been considered by several investigators. G. S. Fraps [74] reports analyses and concludes that cottonseed flour is rich in protein, and, in his opinion, harmless in small quantities. F. Russell [75] notes the former use of cotton seed as foodstuff by the Pima Indians of southern Arizona.

A. C. Crawford [76] concludes that the poisonous principle often present in cotton seed is not an alkaloid, but some inorganic com-

pound, probably pyrophosphoric acid, or a salt of this acid. The harmlessness of certain cotton seeds and cottonseed meals is mainly due to the fact that in them the phosphoric acid exists largely as a compound of ortho and not as one of the other phosphoric acids. Small amounts of pyrophosphates can be borne apparently without injury. It would appear that the kind of fertilizers used and other cultural conditions have an effect on the amount of poisonous phosphoric acid salts present. Whether or not the poisonous properties are derived from the soil or are due to a physiological process in the seeds, and other related matters, the author points out, must be the subject of investigation.

Cottonseed flour was less thoroughly digested than a meat diet containing an equal or greater amount of indigestible nonnitrogenous substances, in experiments by L. B. Mendel and M. S. Fine.[77] The poor showing of the cottonseed flour is ascribed to the presence of a constituent which inhibits secretion or promotes premature evacuation.

W. A. Withers and B. J. Ray[78] have reported tests, including feeding experiments with rabbits, on the removal of toxic properties from cottonseed meal. They extract with gasoline and then boil with alcohol to which a small amount of an aqueous solution of sodium hydroxid has been added. After filtration and washing with hot alcohol and drying, the cotton seed did not exhibit toxic properties.

Of the many summaries of data regarding the composition of foods, mention may be made of a set of 15 colored food charts, prepared by C. F. Langworthy,[79] designed to show graphically the composition and energy value of common food materials and to summarize some general data regarding the functions and uses of food.

SPECIAL STUDIES OF ASH, PROTEIN, AND OTHER FOOD CONSTITUENTS.

While no new food products of special importance have appeared during the period under consideration in this summary, important studies have been made of dairy products, fruits, meats, cereal grains, and other materials, and, as usual, much attention has been given to methods of analysis. No attempt can be made here to summarize the great amount of work done in the inspection of food under national and State pure-food laws. Some reference is made, however, to a number of special studies of ash, protein, and other food constituents.

C. S. Hudson[80] reports a study of milk sugar.

E. B. Forbes[81] investigated the balance between inorganic acids and bases in animal nutrition, the relationship between the mineral elements of food and those of living animal tissues, the production within the animal of inorganic acids and their neutralization, and the relation of ash constituents to human nutrition.

lity of alkali in the ash of human milk was found hat of cow's milk by J. H. Kastle.[82]

ance of sodium and potassium phosphatid compounds derestimated hitherto, according to W. Koch and C. C.

and inorganic phosphorous compounds in meats, especially by cooking, were studied by H. S. Grindley and E. L. by P. F. Trowbridge and Louise M. Stanley[85] and C. K. and P. F. Trowbridge.[86] Phosphorous compounds as brain and related topics were studied by W. Koch.[87] As far as the us system is concerned, he concludes that the use of commercial phorous compounds, including phytin, lecithin, etc., is to be couraged, because there is little evidence that they exercise a vorable effect on the growth of the brain, and because they add ny insignificant amounts of phosphorus to the daily food. If additional phosphorus is desired, phosphorus-rich food, such as eggs, sweetbreads, liver, and some meats, can be used to meet body requirements, though the phosphorus required for brain growth is ordinarily amply supplied by the phosphorus of the daily diet.

Notes on the storage of beef and other food topics are found in a report by H. G. Sharpe.[88]

Iron in the dietary has been studied by H. C. Sherman,[89] who presents a large amount of data regarding the iron content of foods, the amounts consumed in the average diet, and the possibility of increasing the iron content of the dietary when desired by the use of green vegetables and other foods relatively rich in iron.

Calcium, magnesium, and phosphorus in food and nutrition were studied by H. C. Sherman,[90] A. J. Mettler,[91] and J. E. Sinclair.[92]

In general, the investigation shows the importance of calcium, magnesium, and phosphorus in the diet and the possibility of securing these constituents in suitable amounts by the use in proper proportion of ordinary food materials. By the liberal use of milk, or such dairy products as cheese, buttermilk, and cream, it is easily possible to largely increase the calcium and phosphorus intake when this is desirable.

H. C. Sherman and J. E. Sinclair[93] found that, by a proper selection of foods, the net excess of base-forming or of acid-forming elements introduced into the body may be widely varied.

The balance of acid-forming and base-forming elements in foods, and its relation to ammonia metabolism were also subjects of investigation by H. C. Sherman and A. O. Gettler.[94]

The work of T. B. Osborne[95] and associates on cleavage products of protein has been continued. This work includes hydrolysis of excelsin, hordein,[96] legumin from peas,[97] glycinin from soy beans,[98] crystalline globulin from squash seed,[99] amandin from almonds,[100]

proteins from maize,[101] gliadin from rye,[102] vicilin from peas,[103] legumelin from peas,[104] fish muscle,[105] vitellin from hen's eggs,[106] muscle of scallops,[107] crystallized albumin from hen's eggs,[108] ox muscle,[109] casein,[110] and wheat gliadin.[111]

Supplementary to this work, T. B. Osborne and H. G. Wells[112] have investigated the biological reactions of vegetable proteins, using globulin from castor beans, flax seed, and squash seed, edestin from hemp seed, excelsin from Brazil nuts, proteins from coconuts, legumin from the vetch, legumin and vicilin from peas, vignin from cowpeas, glycinin from soy beans, gliadin from wheat and rye flour, hordein from barley, and zein from maize.

Work is reported directly related to that just referred to by Albert G. Emery and Francis G. Benedict[113] on the heat of combustion of compounds of physiological importance, including cane sugar, benzoic acid, dextrose, levulose, lactose, maltose, glycogen, asparagine, aspartic acid, allantoin, alanine, creatine, creatinine, cystin, glutaminic acid, glycocoll, hippuric acid, tyrosine, urea, uric acid, alcohol, acetone, B-oxybutyric acid, lactic acid, glycerin, palmitic acid, stearic acid, and oleic acid.

L. B. Mendel and M. S. Fine[114] have studied the utilization of the proteins of the legumes, the work and other investigations by Mendel and his associates being of great importance in discussions of nutritive value.

Plastein, a proteinlike substance precipitated by enzym action from concentrated albumose solutions, was found related to the higher albumoses and apparently to the antialbumoses rather than to the native proteins by D. D. Van Slyke and P. A. Levene.[115]

PREPARATION, PRESERVATION, HANDLING, AND STORAGE OF FOOD IN RELATION TO NUTRITIVE VALUE.

Chemical changes induced in foods by cooking processes have been investigated with a considerable number of materials and other matters related to preparation, preservation, handling, and storage of food.

United States Commissary General H. G. Sharpe[116] gives data regarding Army rations, field ranges, ovens, fireless cookers, kitchen touring cars, portable gas cookers, etc.

Cooking of beef was studied by Elizabeth C. Sprague and H. S. Grindley,[117] and of spleens by E. T. Williams.[118]

A summary of analytical and other data regarding the economical use of meat in the home, and the nutritive value of meat is presented by C. F. Langworthy and Caroline L. Hunt.[119]

Edna D. Day[120] reports a series of experiments on the digestibility and nutritive value of different starches as affected by cooking. Using different sorts of ferments, digesting experiments were made

with potatoes, wheat, corn, and other starches, with the object of detecting differences in the starches and the effect of heat on the digestibility of starch under common household conditions. The conclusion was reached that potato, arrowroot, and probably tapioca and sago starches are not made more easily digestible by long continued cooking, while the reverse is true with cereal starches, though the change occurs very slightly. Dr. Day [121] also reports the results of experiments on cellulose as affected by cooking.

The possible connection of cooked Indian corn with pellagra was studied by W. H. Buhlig [122] and by J. F. Siler and H. J. Nichols,[123] the corn as cooked being found sterile.

Experiments on setting of gelatin were made by Olive G. Patterson and Clara C. Benson.[124]

Yeast appears to have little or no effect on the flavor of bread according to the experiments reported by Ruth A. Wardall.[125]

Experiments with salt-rising bread were made by Winona Woodward [126] and by H. A. Kohman.[127]

The construction and use of fireless cookers has received considerable attention, one of the most interesting contributions to the subject being that of Ellen A. Huntington,[128] who studied the question from a chemical and physical standpoint.

Many investigators have studied canning, preserving, handling, and storing of food products with reference to nutritive and economic value. A large amount of information regarding commercial conditions, statistics of the production, manufacture, and use of a wide range of commercial food products is included in the bulletins and reports of the United States census for 1910. H. A. Dent [129] has summarized information regarding the economic value of evaporated or dehydrated fruits, vegetables, and milk as used in the United States Navy.

The value of pectin from the white inner skins of oranges and lemons in making jelly is noted by Nellie E. Goldthwaite,[130] who found that such material would yield jelly of good physical quality. The use of citric acid or other natural acid to insure the setting of jelly and other matters of jelly making were also studied.

A study of the influence of preliminary heating, final temperature, and percentage of water, sugar, and acid upon character and quality of guava jelly was made by J. Belling.[131]

H. C. Gore [132] shows that CO_2 may be substituted for sake fumes in rendering persimmons nonastringent, the work being part of an extended series of studies of fruit-ripening problems by the action of acetic acid fumes and many other chemical substances.

The ripening of dates has been studied by A. E. Vinson.[133]

Of the many chemical substances studied it was found that a great many stimulated the ripening of dates. From the diversity of these

reagents the author concludes that the effects observed can not be due to any particular chemical structure, and that many of them do not react chemically with any known constituent of the date. After treatment over night with acetic acid vapor an appreciable reaction for invertase could be obtained in a glycerol extract, although a marked astringency was still present. From these facts and data previously obtained it was concluded that the apparent stimulation of ripening depends solely on the killing of the protoplasm.

In broad terms, any substance which will penetrate the cuticle and kill or stimulate the protoplasm, thereby releasing the previously insoluble intracellular enzymns without rendering them inactive, will bring about ripening, provided the fruits have reached a certain necessary degree of maturity. * * *

Commercially, many varieties of dates may be ripened rapidly after they have reached a certain degree of maturity. Before that time they do not contain sufficient dry matter to make a palatable fruit. Many varieties so ripened are fully equal to the natural product. * * * Fruit of good flavor was obtained by treatment with the vapors of acetic and propionic acids, ethyl chlorid, ethyl bromid, ethylene chlorid, methylene chlorid, and chloroform, and with solutions of lactic, benzoic, and salicylic acids and some other substances of more or less poisonous nature. Gasoline, benzine, esters of organic acids, ordinary ether, acetone, volatile oils, and most other substances leave permanent disagreeable flavors. * * *

Artificially ripened dates do not sour so readily as the fruit ripened on the tree and remain much freer from insects.

Work similar in character has been reported by G. F. Freeman.[134] to commercial value, quality and wholesomeness.

Packing oysters with and without ice, and other similar questions, were studied by the Indiana State Board of Health [135] with reference to commercial value, quality, and wholesomeness.

F. P. Gorham [136] found that the bacterial content of oysters varies with the season, and suggests the necessity of establishing legally a minimum distance between oyster beds which are used as a source of food and sewer outlets.

A. W. Peters and H. A. Mattill [137] studied the diastatic enzym of ripening meat.

No deterioration was found in frozen beef stored for a long period in experiments by W. D. Richardson and E. Scherubel.[138] Other experiments tending to show the value of cold-storage beef practically equal to that of fresh beef were made by A. D. Emmett and H. S. Grindley.[139]

S. Rideal [140] finds that cold storage retards, but does not prevent, action of diastase, and that tenderness is increased by the action of sarcolactic acid, and by pepsin and trypsin.

Studies of methods of handling and storing poultry with reference to food quality have been made by Mary E. Pennington,[141] by W. F. Boos,[142] by H. R. Brown,[143] by E. W. Burke,[144] by H. W. Wiley et al.,[145] and by H. W. Houghton.[146]

The occurrence and permanence of lipase in the fat of the common fowl have been studied by Mary E. Pennington and J. S. Hepburn.[147]

Several studies have shown the advantages of wrapped bread over unwrapped with respect to moisture content and quality, as well as sanitary condition. Among others, are those of L. W. Thomas[148] and C. A. A. Utt.[149]

That well-lighted rooms will retard the growth of fungi and bacteria in stored flour is the conclusion of H. G. Bell,[150] who studied the question chiefly with reference to quality.

The effect of storage on flour and on butter was studied by J. T. Willard,[151] particularly the variations in water content under different conditions of handling.

S. Leavitt and J. A. Le Clerc[152] determined the changes which take place in the composition of stored cereals.

DIETARY STUDIES AND DIETETICS.

Descriptive articles, books of travel, reports of ethnological investigations, and other publications not directly concerned with nutrition work contain valuable information about dietary habits, food supply, and living conditions of native tribes. Numerous volumes and papers of this character have appeared during the period under consideration. Furthermore, a very great number of dietary studies have been made and reported. In some of these publications analyses of foods are reported and, in general, the facts presented are considered on the basis of nutritive and economic value.

Dietary studies of farmers' families in Vermont, Tennessee, and Georgia were made as part of the nutrition investigations of the Office of Experiment Stations. Cost of nutrients and energy, peculiarities of diet, adequacy of food supply, and similar questions are considered.[153]

European laborers in the Panama Canal Zone consumed food which supplied 201 grams of protein and 5,428 calories of energy per person per day, according to data in the report of E. T. Wilson.[154]

Information concerning the cost of food under local conditions is also given in this report. The cost of materials (including ice) was found to be 30.18 cents per man per day, and the expense of preparation, etc., to be 6.66 cents per ration in addition.

Studies of native dietaries in the Philippines have been made by E. D. Merrill,[155] by H. Aron,[156] and by V. G. Heiser.[157]

The value of studies of the dietaries in public institutions is being more and more thoroughly appreciated, as is evidenced by the numerous requests for such investigations received by the Division of Nutrition Investigations of the Office of Experiment Stations.

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by Ellen H. Richards,[178] and by

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alytical work was carried on as part of the studies of
nd nutritive value of legumes by C. E. Wait,[184] which
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ISM EXPERIMENTS, INCLUDING STUDIES OF INCOME AND OUTGO, MADE WITH RESPIRATION CALORIMETERS.

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of food constituents, particularly nitrogen, have appeared, in-
ling special studies of body excretions, the effects of food con-
tuents, and other effects of protein metabolism, the effect of water
rinking on physiological activities, including the utilization of food, and many studies of income and outgo of material and energy. Some of this work has a direct relation to the question of nutritive value of foods, since it was undertaken to test this matter from the standpoint of utilization rather than analysis. Reference will be made here to only a few of the investigations, which will serve as illustrations of the kind of work undertaken.

The dietary of a hospital for the insane in Illinois, at which there had been an occurrence of pellagra, was found by J. F. Siler and H. J. Nichols [158] to supply about 30 grams of protein and 2,000 to 2,500 calories per person per day. The diet was studied with reference to cost and nutritive value, as well as matters of hygiene.

A comprehensive and exhaustive study of dietaries in State institutions was made by H. C. Wright,[159] particular attention being given to methods of purchase and other effects of cost.

In experimental studies on growing dogs and observations on nursing children, H. Aron [160] found that with a dietary insufficient to permit of increase in body weight, the skeleton grows at the expense of other parts of the body, especially of the flesh, most of the organs retain their size and weight, the brain grows to normal weight, fat is consumed almost entirely, protein in the muscles is decreased in quantity, and a great proportion of the tissues is replaced with water.

The relation of the diet to body growth has been studied by H. J. Waters [161] and by D. McCay,[162] the latter especially noting the relation of quantity of protein in the dietary to average body weight of certain races. All this work bears directly on the nutritive value of the ration and the foods of which it is composed.

Dietaries of children in public institutions have been studied by the Department of Agriculture.[163] Much information regarding the feeding of children, school luncheons and other matters of normal diet, and problems of undernourishment of children has been reported, the nutritive value and cost being considered as well as physiological aspects of the problem. Papers on such topics may be mentioned by Caroline L. Hunt,[164] by the Women's Educational and Industrial Union,[165] by Lillian D. Wahl,[166] by Marion Bell,[167] by E. M. Sill,[168] by Frances Perkins,[169] by W. C. Hollopeter,[170] by H. H. Bonnell,[171] by Alice C. Boughton,[172] by Ellen H. Richards,[173] and by A. L. Benedict.[174]

Many special dietary problems have been investigated, a few of which may be cited.

I. Fisher [175] finds a relationship between protein consumption and the occurrence of fatigue.

No relation between muscular activity and protein metabolism, as indicated by nitrogen and sulphur partitions in the urine, was found by P. A. Shaffer.[176]

An experimental study of an ash-free diet by H. W. Goodall and E. P. Joslin [177] did not reveal any marked changes in metabolism as compared with an ordinary diet.

In a discussion of an endurance test, in which a number of men endeavored to carry 100 pounds weight on the back for 100 miles, C. F. Langworthy [178] notes that the average energy expenditure of the six successful contestants was 1,137 calories, 707 calories of which,

it was calculated, were expended in forward progression, and 430 calories in moving the load.

DIGESTION.

Both thoroughness and ease of digestion have been studied, the latter in many cases with the aid of the respiration calorimeter, and many special topics relating to digestion have been discussed.

The Office of Experiment Stations, as already noted, has studied the thoroughness of digestion of cheese. Work was later undertaken to secure data regarding the relative energy output during the digestion of cheese and meat, the respiration calorimeter being used for these experiments. The work which is being continued has been briefly noted in the Yearbook of the Department of Agriculture by C. F. Langworthy and R. D. Milner.[179]

No constant differences were observed in the energy output of the subject when digesting cheese and when digesting an equivalent amount of meat under uniform conditions.

The relation of temperature of coagulation to digestibility of white of egg was studied by P. Frank.[180] Heating above 75° C. decreased digestibility.

Practically no difference in thoroughness of digestion of different cuts of meat prepared in different ways was found by H. S. Grindley,[181] T. Mojonnier,[182] and H. C. Porter,[183] all meats being found very digestible, about 98 per cent of the protein and fat being retained.

Extended analytical work was carried on as part of the studies of digestibility and nutritive value of legumes by C. E. Wait,[184] which has already been referred to. In general, legumes were found to contain 70 to 83 per cent digestible protein and 98 per cent digestible carbohydrate.

METABOLISM EXPERIMENTS, INCLUDING STUDIES OF INCOME AND OUTGO, MADE WITH RESPIRATION CALORIMETERS.

During the period under consideration many studies on metabolism of food constituents, particularly nitrogen, have appeared, including special studies of body excretions, the effects of food constituents, and other effects of protein metabolism, the effect of water drinking on physiological activities, including the utilization of food, and many studies of income and outgo of material and energy. Some of this work has a direct relation to the question of nutritive value of foods, since it was undertaken to test this matter from the standpoint of utilization rather than analysis. Reference will be made here to only a few of the investigations, which will serve as illustrations of the kind of work undertaken.

The nutritive value of nitrogen in gelatin was studied by J. H. Murlin,[185] who concluded that nitrogen equilibrium may be maintained when part of the proteid nitrogen is replaced by gelatin nitrogen, provided a large proportion of the total energy is supplied in the form of carbohydrates. Similar work with gelatin has been reported by P. A. Levene and G. M. Meyer.[186]

An experimental study of nuclein synthesis in the body was made by E. V. McCollum.[187]

Extended studies of the nutritive and economic value of foods, particularly with reference to the low proteid diet, carried on by R. H. Chittenden and his associates represent an important contribution to the subject of nutrition, involving as they do the consideration of the question of physiological and pecuniary economy.

Extended studies on the effects of water drinking by Hawk and his associates at the University of Illinois, the experiments by Mendel and others at the Sheffield Scientific School, Yale University, and other work which might be appropriately cited, will undoubtedly be considered at this conference in other sections.

The possibilities of nutrition investigations were very greatly extended by the successful attempts made by W. O. Atwater and his associates to devise a respiration calorimeter, an instrument of precision for the simultaneous measurement of the income and outgo of matter and energy. After several years of work carried on by him for the Office of Experiment Stations cooperating with a number of agencies, the apparatus was perfected for use in experiments of long or short duration with man, and the results of many experiments with it reported from time to time very largely in documents published by the United States Department of Agriculture.[188]

More recently, the original apparatus devised by Atwater and his associates has been modified and improved at the United States Department of Agriculture, in connection with the nutrition investigations, which have grown out of the older cooperative enterprises of the department; at the nutrition laboratory of the Carnegie Institution of Washington, which is located in Boston, Mass.; and at the Cornell Medical College in New York City. The apparatus has also been adapted to experiments with farm animals (cattle) by Armsby[189] at the Pennsylvania State College, and is employed in experiments carried on by that institution in cooperation with the Bureau of Animal Industry of the Department of Agriculture.

A brief description of the respiration calorimeters in use in the Department of Agriculture at Washington is given by C. F. Langworthy and R. D. Milner.[190] A large calorimeter for experiments with man, an improved and smaller one for the study of physiological processes of plants and animals by means of the gaseous exchange and heat production, and a microcalorimeter for the experi-

mental study of very small quantities, are described, as well as several new devices for recording and controlling the operation of the apparatus. Some consideration is given to the character of the problems which the new apparatus will, it is hoped, aid in solving. A later paper by C. F. Langworthy and R. D. Milner[191] describes the construction of the smaller respiration calorimeter in greater detail.

The improved forms of respiration calorimeters used at the nutrition research laboratory of the Carnegie Institution at Boston, Mass., are described in detail by F. G. Benedict and R. M. Carpenter.[192] Control tests made by burning alcohol in the respiration chamber, and measuring the carbon dioxid, water, and heat produced, and the oxygen consumed, showed a satisfactory agreement with the amounts required theoretically. These tests are detailed by F. G. Benedict,[193] J. A. Riche,[194] and L. E. Emmes.[195] Methods for determining the amount of oxygen consumed in experiments with the respiration calorimeter are discussed by F. G. Benedict.[196]

A simple apparatus for the study of respiratory exchange is also described by F. G. Benedict.[197]

As an example of work which has a direct bearing on nutritive value of foods carried on at the Carnegie Nutrition Laboratory, a paper by F. G. Benedict, L. E. Emmes, and J. A. Riche[198] may be cited in which the results showed that there was a high respiratory quotient 12 hours after the ingestion of a meal rich in carbohydrates.

Lusk[199] has very briefly referred to the construction of the respiration calorimeter which is used under his direction at the Cornell Medical College for the study of problems pertaining to the nutritive value of foods and related questions. The experiments so far have been made particularly with laboratory animals and with children.

HYGIENIC STUDIES OF FOODS IN RELATION TO THEIR ECONOMIC VALUE.

There has been a noticeable tendency toward a fuller recognition of the value of cleanliness in all that pertains to the handling, marketing, preparing, and serving of food, and such questions and other problems of food hygiene have been the subject of many careful studies. Such work has a more direct bearing upon the economic value of food than upon its nutritive value, as shown by chemical composition.

In the study of the use of sour milk preparations to inhibit intestinal putrefaction, etc., P. G. Heinemann[200] found the commercial preparations of lactic acid bacilli in no way superior to those of natural souring. Only one of the commercial preparations was found free from yeast. Many other studies which have to do with the relation of lactic acid or other food constituents to intestinal putrefaction have been studied.

A bacteriological study of protected and unprotected foods in shops and restaurants was made by H. E. Barnard.[201] In this case also the paper cited serves simply as an illustration of many others which might be mentioned, and the same is true of the works of C. W. Stiles,[202] who studied the danger of sewage contamination of oysters.

M. Steel[203] has studied the absorption of aluminum from aluminized food. Later work on the subject has been reported by W. J. Gies,[204] particularly with reference to aluminum salts added to food in alum baking powder, a matter which manifestly has an effect upon the quality and value of food.

The effect of edible fats and oils on metallic containers made of tin plate, galvanized iron, copper, tin, lead, zinc, aluminum, and iron was studied by J. A. Emery.[205]

The alleged relation of Indian corn to pellagra has a decided bearing upon the economic value of corn, as it does upon the use as food of this standard cereal crop. The problem has been investigated by C. L. Alsberg,[206] C. H. Lavinder,[207] W. H. Buhlig,[208] and J. F. Siler and H. J. Nichols.[209]

The investigations which have had to do with rice and beriberi have been mentioned elsewhere. Many other investigations might be cited under the heading of hygiene and its relation to food and its nutritive value, but enough has been noted to show the general character of the American work.

COST AND ECONOMIC VALUE OF FOOD AND OTHER STATISTICAL DATA.

The collection of statistical data, an important part of the general subject of nutrition, has been carried on quite extensively by the National Government and by different States, as well as by economists and other investigators. The investigations cited give an idea of the character and extent of the work, but attempt is not made to make this summary exhaustive.

A compilation of publications on the cost of living and prices has been made by H. H. B. Meyer.[210] Similar data may be found in various Senate documents.[211]

Many studies of the production and value of food products have been made in connection with the work of the United States census. Among them are those on rice cleaning and polishing by H. McK. Fulgham;[212] beet sugar, by Z. C. Elkin;[213] slaughtering and meat packing;[214] and starch, by R. H. Merriam.[215]

A summary of retail prices of food from 1890 to 1906 and a discussion of cost of living appear in a publication of the United States Bureau of Labor.[216] Cost of food in New Jersey is discussed in a report of that State.[217]

Meat prices in the United States are summarized in the Yearbook of the Department of Agriculture, by James Wilson, Secretary.[218]

Statistics of Hawaiian honey production may be found in a paper on Hawaiian bee keeping, by E. F. Phillips.[219]

Cost of living of wage earners and a discussion of rational diet at small cost are included in a report of the Committee on Social Betterment, by G. M. Kober.[220] See also Alimentation and Foods.[221] Reference has already been made to Wright's studies on the effect of methods of purchase, on cost of food in public institutions, and related matters.

An investigation into the cost of living of workmen's families was made by R. C. Chapin.[222] Valuable work of this character has also been published by the Bureau of Labor of the United States Department of Commerce and Labor.

A study of the cost of living conditions in American towns was made by the British Government[223] and reprinted in the United States by the Federal Government.[224] The report was summarized in a United States Senate publication,[225] and also in a Department of Commerce and Labor publication.[226] Twenty-eight American towns, with an aggregate population of 15,500,000, were studied to secure data on which to base conclusions. Prices ranged from 91 to 109, New York City prices serving as a standard and rating as 100. Average retail prices were found about 38 per cent higher than in England and Wales. The dietary of workingmen in this country was found more liberal and varied than in the United Kingdom. The report, as a whole, is a very important contribution to the literature of food costs.

An extended investigation of food prices, the conditions of manufacturing and marketing, and related questions pertaining to the cost of living has been made by a special commission appointed by the State of Massachusetts. Their report[227] contains a great deal of valuable data on the cost of food and on conditions of manufacture, handling, and storage with reference to value from an hygienic standpoint as well as cost. The report of the commission[228] appointed by the State of Massachusetts to investigate the subject of cold storage of food and of food products kept in cold storage should also be mentioned as an important contribution to a question of great economical importance.

General discussions of topics pertaining to the nutritive and economic value of food have been very numerous and have included many textbooks and works of reference, as well as pamphlets and short articles. To this large amount of material it does not seem possible to refer in detail at the present time.

AGENCIES FOR MAKING INFORMATION AVAILABLE.

No summary of American work on the nutritive and economic value of food would be reasonably complete which did not make some

reference to the agencies which are employed for disseminating information and making it available to the public, as well as those employed in obtaining it. Articles and reports already cited show that such material is generally published in readily accessible form.

Boards of health of different States, city boards of health, and other similar agencies have devoted much time and money to gathering and disseminating information concerning the real value of food as distinguished from its market price, the importance of clean food, and other similar matters.

It has been the policy of the Federal Government to distribute its publications without cost to those who have need for them, and this applies, in many cases, not only to summaries designed for popular use, but to technical bulletins. The Department of Agriculture is undoubtedly the largest distributer of such popular documents, and the total number of those dealing with various questions related to the nutritive and economic value of food, pure-food supplies, and such topics, has reached many millions.

Public schools and higher institutions of learning are devoting much time to instruction in nutrition and other home economic topics. The question of food values, methods of preparing food, and so on, is very generally a part of a girl's high-school work, upwards of a thousand high schools in the United States offering instruction of this character. Over a hundred agricultural and other colleges offer advanced instruction in home economics which includes nutrition, as well as more than a hundred normal schools and other special schools. The character and extent of this work has been described by Marie T. Spethman.[220]

Any widespread interest in the serious study of a problem usually results in the formation of a society or association of those interested, and this has been the case with nutrition. The American Society of Biological Chemists, the American Chemical Society, and other societies have sections devoted to the consideration of food and nutrition problems, and much interest in such subjects on their economic side is manifested by economists and sociologists. The association which gives attention particularly to the consideration of problems of food, clothing, and shelter, in their various relations, is the American Home Economics Association, which was established in 1909, and includes in its membership a considerable body of investigators and teachers, as well as those who are interested in the application in the home of the results of scientific investigation.

CONCLUSIONS.

The purpose of the foregoing summary of work, which has to do with the composition and nutritive value of food, carried on in the United States since the preceding Congress on Hygiene and Demog-

raphy, in 1907, is to give an idea of the character and extent of the work and examples which will serve to show something of the results obtained.

The summary is by no means complete, but it is believed that enough has been brought together to show that continuous progress has been made in devising and perfecting methods of research and in accumulating data valuable to workers in nutrition. It is also apparent, from a study of the data, that the whole question of the nutritive and economic value of food is receiving a great deal of attention in the United States, and that interest is widespread in the attempts made to collect and distribute information which will lead to a rational and intelligent use of available food resources.

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THE CHOICE OF FOODSTUFFS IN RELATION TO DISEASE.

Dr. CARL VON NOORDEN, Professor of Internal Medicine and Director of the First Medical Clinic, Vienna, Austria.

The task I have undertaken is concerned with the question as to what influence the choice of foods has on the course of disease; or, in other words, to what extent the selection of special foodstuffs is a valuable therapeutic factor in the treatment of certain diseases or groups of diseases.

The subject can, of course, be approached from various points of view. We might start with certain articles of diet or with certain groups of foodstuffs, and then by working out the characteristic facts with regard to their assimilation and the way in which they are utilized in the organism, we might easily determine under what special morbid conditions they would be found useful and under what other conditions we should expect them to be of little or no value. Specialists in hygiene or physiology would perhaps select this course. As a physician, however, another method comes to me more naturally. We will start with certain groups of diseases and satisfy ourselves as to the special dietetic problems which they involve; we shall then be in a position to state which foodstuffs will be of value toward the attainment of our object and which will be the reverse. Of course, in the short time at my disposal I shall not be able to go into details and I shall be unable to deal with the most important question of the preparation of foods and drinks. At the same time this is very important in dietetics and most fruitful in results. I can only deal with the large groups of foodstuffs, such as proteins, fats, carbohydrates, aromatic bodies, and so on, and accurate detail will only be possible here and there.

1. OBESITY.

Our first subject will be obesity, or rather the measures which are useful in combating this condition. All the dietetic cures for obesity have one underlying principle in common, namely, to decrease the bulk and the calorific value of the food. It was formerly thought that certain foodstuffs were specially bad for the corpulent or the reverse. We now know that this is not true. The amount of fat gained or lost by the body depends ultimately on the ratio between its requirements in calories and the actual supply. The particular food selected is of subordinate importance if its caloric value is correctly determined. In spite of the fact that this principle is theoretically irrefutable in practice, our results will vary according to the manner in which it is applied. Perhaps the most natural thing would be to restrict equally all the three chief groups of foodstuffs—

carbohydrates. Experience, however,
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to cover his real needs, and thus slowly
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re, as we know from Voit's fundamental work
are excellent sparers of body proteins. Of course,
tion or even the entire exclusion of fat will not
ient, and where a rapid decrease in weight appears
uctions as to the amount of the remaining foodstuffs
required. These are very efficacious, but not altogether
for obesity, which require special supervision on the part
ysician. These are the so-called rapid cures which formerly
bad a reputation because they caused so much exhaustion. I
e that the bad consequences of these rapid cures can be entirely
led if it is clearly laid down that while the fats are reduced to a
nimum there should still be a considerable amount of carbohydrate
n the diet, even when the total quantity of food is largely diminished. The fats necessary for oxidation are easily taken by the organism from the natural fatty cushions of the body.

The knowledge gained from theoretical and practical or empirical sources of the importance of allowing large amounts of carbohydrates in obesity cures has recently led to the recommendation of an exclusively vegetable dietary.

I have carefully followed the practical results of this attempt and put together some original observations on the subject. My opinion is not in its favor. A satisfactory loss of weight is attained by this

method, but in a large number of cases there is also a very undesirable loss of strength and marked anemia, which, it is more than probable, we must attribute to the relative poverty in proteins of a vegetable diet. According to my very extensive observations the best results are obtained in obesity cures when fats are most completely excluded and at least 120 grams of protein are taken. As regards the amount of carbohydrates for rapid cures, at least 120 to 150 grams should be allowed per diem; when, however, rapidity is of no importance, the amount of carbohydrates can be considerably larger. To a learned audience I need not insist on the fact that the amount of water ingested is entirely without influence on the process of fat reduction. However, the reduction of the intake of water may be of great therapeutic consequence, where it is necessary not only to reduce the deposit of fat, but also to fight against disturbances of the circulation.

2. OVERFEEDING.

The reverse of obesity is represented by those frequent cases in which it is the aim of the medical art, and especially of dietetics, to improve the condition of nutrition. The causes which lead to nutrition either becoming or remaining insufficient are highly complex and will not be further considered here. When we prescribe overfeeding for any individual we must be quite clear in our minds that by increasing the dietary we are, in the main, only increasing the amount of fat in the body. Of course, proteins are well stored in the body, but even under the most favorable circumstances their amount is very small compared to the increase in fats. Moreover, it is very questionable whether the nitrogenous substances which are retained during overfeeding really produce an increase in the living protoplasm. Probably the greater part of them only represent reserve material which the cells accumulate in the same way as they do the particles of glycogen and fat. It appears that the storing of the proteins takes place more abundantly when large amounts of protein are included in the increased dietary, and especially when much casein and its derivatives are given. Practical experience, however, prevents us from drawing a valuable lesson from this fact. Nearly always we have to deal with persons of small appetite, and we know empirically that the abundant use of proteins markedly decreases their capacity for the input of other foodstuffs.

In overfeeding we can seldom give more than 100 to 120 grams of protein, and we should fail in attaining the object of the cure if we forced the patient to take more than this amount. With regard to the nonnitrogenous foodstuffs our attention must first be directed to the carbohydrates. We know that by the help of these

substances we can produce a protein increase quite as well as we can by means of the albuminoids—perhaps even in a better and more permanent manner. For this reason a considerable amount of carbohydrate is included in all cures by overfeeding. But the limit is soon reached; nearly all carbohydrates require considerable dilution in order to make them palatable. With few exceptions the carbohydrate foods ready for eating occupy a considerable bulk, and they therefore satisfy the patient's appetite sooner than the conditions of the cure require. I have shown that in a large number of cases it is exceedingly difficult in overfeeding to raise the daily total of carbohydrates above 250 or 300 grams. With the quantity of protein mentioned above this amounts to a caloric value of about 1,200 to 1,400. From this we can of course expect none of the results of overfeeding, so that all the positive results of the cure must, in the end, depend on the amount of fat which can be combined with the proteins and carbohydrates. It is indeed no easy task to introduce the wished-for amount of fat without arousing the resistance of the patient. In this connection great attention must be paid to the culinary department. In overfeeding cures as usually carried out in my clinic, we succeed on the average in getting 300 grams of fat ingested, which represents a total of more than 2,700 calories, and is a substantial foundation for large and rapid results. It is only with the help of such a large amount of fat that we have succeeded in securing an average increase in weight of 2 kilograms per week during our cures by overfeeding.

We can thus see that in both these opposing dietetic cures of reduction and overfeeding the result depends essentially on the amount of fat which is ingested, in the one case by its greatest possible restriction and in the other by its greatest possible increase.

3. GOUT AND THE URIC ACID DIATHESIS.

I may now consider another metabolic disorder, namely, gout and the uric acid diathesis. The matter is comparatively a simple one. We know that human beings produce a certain amount of uric acid during the ordinary work of their tissues; this uric acid is termed "endogenous." We can not influence its quantity by any of the usual methods at our disposal; we only can bring about conditions which favor its better elimination. The remaining portion of the daily production of uric acid is derived exclusively from the purin bodies of the foodstuffs; this portion is termed "exogenous." We know that purin bodies occur partly in the nuclei of the cells and partly as extractive bodies of the tissue juices.

In persons with gouty tendencies the amount of food containing purin bodies must be carefully controlled. When gout is fully developed, it may be necessary to limit the dietary to vegetable foods,

or to animal foods which do not contain the stuffs for the formation of uric acid, such as milk, milk preparations, and eggs. However, it is only in the worst cases that such a rigorous diet is absolutely essential. Many gouty individuals are able to tolerate a certain amount of purin bodies in their food. The quantity of these substances ought to be pointed out in each case if the patient is to be protected from dangers. Seven years ago, in a lecture at Chicago, I brought forward and described such a tolerance test.

Other dietetic considerations are not of such fundamental importance in the treatment of gout. Of course, in many cases, complications such as excessive obesity, or gastric, intestinal, or cardiac troubles may arise, but these underlie the usual dietetic directions and have nothing to do with the primary metabolic changes in gout, which are chiefly concerned with the intake of purins.

4. DIABETES MELLITUS.

In this frequently occurring and important disorder of metabolism, matters are by no means so simple. The time at my disposal will not allow me to discuss this condition at great length; a lecture of many hours' duration would hardly suffice for anything like a full consideration. An excessive activity of the sugar-forming function of the liver is a chief feature in diabetes. More sugar is formed than the tissues can assimilate. The greater the activity of the sugar-forming apparatus, the greater the manifestations of diabetes. Our efforts must be directed, therefore, to diminish the abnormal activity. The most important excitants of the sugar-forming functions are the carbohydrates of the food, and we are called upon to restrict these as much as possible.

It has become almost an axiom that we must diminish or exclude carbohydrates from the dietary in order to decrease the sugar output in the urine, but we know to-day that this is only a matter of secondary importance in diabetic treatment, and that it is much more important to treat the causes of the glycosuria and hyperglycaemia, i. e., to diminish the abnormal activity of the sugar-forming processes. Hence, the prohibition of carbohydrates appears in a new aspect—one which is more rational and important than the older views. We understand now the healing influence of a long period of carbohydrate starvation; we thus exclude the harmful influence of continuous stimulation of the sugar factory. The researches of recent years have taught us that proteins also act as powerful excitants on the sugar factory. It is not so much, it appears, a matter of the carbohydrate moiety of certain proteins or the formation of sugar from the amino-acids of the protein molecules as the fact that it is the chemical work of the liver, necessary for the assimilation

and disintegration of protein bodies, which acts as a stimulant to the sugar-forming processes. I may venture the statement that while carbohydrates supply the nutriment for a working animal, the proteins act as a whip. Both result in the production of considerable energy, but the ways are different. Practical experiences teach us that the various proteins differ in their powers of exciting the production of sugar; for instance, the protein of meat and milk stimulate it more than that of eggs and of vegetables. We have also learned that the administration of proteins and carbohydrates at the same time is followed by a greater sugar output than when they are given separately with a few hours' interval between the meals.

Investigations upon the respiratory exchange in diabetes have shown that the detrimental effects of protein upon the metabolic functions of diabetics are chiefly related to the specific dynamic influence of protein upon the total metabolism. In healthy individuals this influence is but slight and only assumes importance under special sets of conditions (Rubner), but when the processes of oxidation are increased the influence becomes distinctly recognizable. To-day we know, indeed, through the valuable researches of Benedict, Joslin, and Falta, that in severe cases of diabetes the total oxidation processes show a marked increase. A practical consequence of this is that we no longer prescribe such large amounts of albumin, and especially of meat, as we at one time did, and it is a marked step forward to be able to say that under such conditions a larger amount of carbohydrates are admissible. The researches which I published some 12 years ago showed that by the entire exclusion of meat from the dietary it was even possible to allow the diabetic patient for a while to take an enormous quantity of carbohydrate. A number of comprehensive investigations have revealed the fact that under such conditions the starch present in oaten foods is the most favorable one. Next in order comes banana meal, large quantities of which have been kindly supplied to me for the purpose of research by the American Department of Agriculture. Of less value, but still of practical utility for the diabetic, when meat is excluded, are wheat, rye, and potato starches. These differences in the assimilation of the various carbohydrates are very remarkable, and as yet we have no satisfactory theory to advance as an explanation thereof. The facts, however, are incontrovertible and possess great importance for the therapist.

5. FEVER AND GRAVES'S DISEASE.

Certain conditions, associated with a general increase of the total metabolism, present a somewhat similar picture to that of diabetes. They are, if we neglect the rarer diseases, febrile conditions and

Graves's disease. It has long been a matter of everyday experience that patients with fever do not stand meat food well and that this defect is not so much due to changes in the digestive organs as to the peculiar influence of meat on the general condition and on the temperature. Similarly, in thyroid disease a diet containing little meat is better for the patient than one containing much meat, especially at the period when there is a tendency to emaciation. This was empirical treatment at one time, but now, owing to observations made in my clinic, it has been placed on a sound basis, for it has been shown that in these patients the specific dynamic effect of albumin, and especially of meat, is much greater than in the healthy. I believe that this little recognized, and by some denied, effect of the specific dynamic influence of various foodstuffs is of greater importance for the sick than for the healthy and calls for further inquiry.

6. DISEASES OF THE STOMACH AND INTESTINES.

I turn next to the diseases of the digestive organs. Naturally, in these conditions the choice of food is of great importance. If I restrict the discussion, in accordance with my introductory sentences, to the significance of the selection of proteins, fats, and carbohydrates in the therapy of these diseases, I may consider the available facts under one heading.

In the majority of the digestive disorders it is possible to utilize the most of the various types of proteins, fats, and carbohydrates, and the art of the physician consists only in the right mingling of the foodstuffs and in the right measuring of the relative quantities of each and in instructions for their proper preparation for consumption. This is more a question of culinary technics than of metabolism. The individuality of the patient also is a matter which calls for special attention in gastric and intestinal troubles, perhaps even more so, than actual scientific hard-and-fast rules. Therefore the success of the treatment depends largely upon the personality of the physician. The intuition which enables the appreciation of the outstanding features and capacities of the individual patient is not given to everyone. However, some directions may be of value. I may shortly remind you that when the hepatic or pancreatic secretions are obstructed, and so do not play their part in the intestine, fat is badly digested and important disturbances result. The view that fatty foods also are harmful in gastric diseases had gained a wide acceptance, but except in acute gastritis it is not really so. The difficulty may be easily overcome by selecting the right type of fatty food and preparing it in a suitable manner. This statement is now perhaps chiefly of historical interest, for it is quite 20 years

ago since I first called attention to this fact. (Berliner Klinik, Heft 55, 1893.)

Less well known is the effect of the mixture of meat and carbohydrate. Many patients suffering from chronic constipation or chronic or recurrent diarrhea exhibit marked improvement when meat or carbohydrates are given separately, whilst the same foods given together appear to aggravate the conditions. We may remember that there are many bacteria which yield different fermentation products when incubated upon a medium containing protein only, from those when grown upon a mixture of protein and carbohydrate. One of my assistants, H. Eppinger, has found that in some stools there are bacteria present which, when grown upon a protein-carbohydrate medium, produce poisons which are harmful to the autonomous nervous system. Clinical experience has shown that while in some cases unfavorable effects are produced by a mixture of milk with the disaccharides, such as milk sugar and cane sugar with meat, such effects are avoided when a monosaccharide replaces the other sugars. The monosaccharide is absorbed before it harms. It is a significant fact that in the old Mosaic law one finds the enactment that milk and meat shall not be eaten together. The many observations of the harmful effects of this mixture justify the Mosaic rule.

An interesting and little recognized clinical picture sometimes is associated with chronic constipation. The patient complains of pains in certain nerve areas and the symptoms are frequently put down to rheumatism or gout. A careful examination shows, however, that there is a widely spread neuritis and one which must be considered as an "elective neuritis" of the sensory nerves. The urine contains a large amount of indican—frequently four or five times the normal quantity. All the ordinary forms of treatment, such as hot baths, electricity, drugs, etc., prove useless. We may not wonder at this, for it is a toxic neuritis of intestinal origin. The neuritis disappears with astonishing rapidity when the abnormal intestinal decompositions are stopped. To produce the alteration in the intestinal fermentation may require some considerable time and may call for the trial of many dietetic methods before a successful result is attained. In some specially interesting and typical cases it is necessary to prohibit meat foods for many weeks and to give large quantities of milk (or better, "yoghurt"), whereby the fermentations yielding indol and skatol may be safely repressed. If this treatment be continued sufficiently long a return to a meat diet may be permitted. In the meantime the bacteria responsible for the abnormal fermentative changes will have disappeared. I mention this method as an example only, for it does not suffice in all cases. Sometimes an entirely different dietary must be chosen. The relationships of certain definite proteins

and carbohydrates appear to possess important and weighty therapeutic powers. I hope during the course of the next few years to publish the results of an extended investigation upon the subject. The difficult bacteriological experiments require considerable time, although the therapeutic effects in the frequent, stubborn, and painful type of enterogenous neuritis already are quite evident to me.

4. DISEASES OF THE KIDNEY.

I have chosen for the last group of diseases on which I shall speak the diseases of the kidney. Of the three principal groups of foodstuffs, the proteins, the fats, and the carbohydrates, the protein is the only one of special significance in diseases of the kidney, for the more protein that is broken down in the body the more will the kidneys be tired out with work. The fact that medical practice has for a long time insisted on the value of a minimum intake of all forms of protein in nephritis, is a special expression of the general view that damaged organs require the greatest possible amount of rest. We now know through the fascinating researches of Chittenden that a diet poor in proteins can be borne much longer and much better than was formerly thought to be the case. Moreover, the necessity for protecting the kidneys demands that extractives and all spices which are to be excreted by the kidneys shall be reduced to the smallest possible amount. I can not now go into details. It is, however, comparatively recent that we have learned that this does not represent all that we can do for the protection of the kidneys. The enormous amount of work undertaken by the kidneys in the excretion of water and salts was not formerly sufficiently appreciated. From the point of view of the expenditure of energy it is markedly greater than the work involved in the excretion of the organic products of metabolism. For this reason, in many cases of nephritis it is necessary on the one hand to order a diet poor in common salt, and on the other to restrict the intake of fluids. Frequently it is necessary to combine both these methods; in some cases the greatest stress must be laid upon reducing the fluids, and again in others upon limiting the common salt. The latter is most important when a true inflammatory or degenerative process is evident in the organ; whereas the diminution of the fluid intake is of great and especial use in those much more numerous cases in which disease of the vascular apparatus of the kidneys dominates the clinical picture.

I will now conclude the review, which I wish to present of the relations of disease to the selection of foodstuffs. I have had to refrain from going fully into the clinical details which make the questions we have raised so full of interest. The deeper we probe these questions the broader and firmer appear those great principles

which I have here endeavored to lay down; but, on the other hand, we are always learning to appreciate fresh difficulties which warn us not to adopt an attitude of rigid dogmatism. Almost every case of disease teaches us that there are limits to scientific dietetics. At the bedside we have to deal not only with diseased organs and disturbances of particular functions, but with sick people; and therefore we have to consider all the characteristics which a person has developed in the course of years and which differentiate him from the generality of mankind. This is, unfortunately, often forgotten, and it is an everyday experience that hard and fast dietetic rules are laid down and carried out which only regard the name of the disease and do not take any account of the individuality of the patient. The art of the physician begins at that point where the principles of dietetics have to be brought into correspondence with the special characteristics of the particular case. It is only when both a knowledge of the dietetic data and the individualizing art go hand in hand that the therapeutics of diet can display the powers with which it really is endowed.

DIET IN RELATION TO DISEASE.

AXEL HOLST, Professor of Hygiene, University of Christiania, Norway.

Apart from the diseases produced by microbes or substances of a general poisonous nature, our diet can become injurious because it contains too much, or, vice versa, because it contains too little, of certain constituents.

In a short paper it is impossible to enter into all details of this important chapter of pathology. As far as "too much" is concerned, I therefore limit myself to summarize the well-known facts, that if we take too large quantities of food, the metabolism may be unequal to the task, or the functions of the stomach and intestines may be injured. Chiefly, though not always, this concerns predisposed individuals. How an overfeeding may produce adipositas nimia and perhaps a fatty liver; how it affects children fed on artificial food ("Milchnährschäden" and "Mehlnährschäden" of the Germans) and may, in connection with the influence of the summer heat, produce many cases of summer diarrhea; how the "purines," being harmless to normal people, may produce arthritis urica in predisposed persons; how the same applies to the influence of carbohydrates on diabetics; how albuminous substances may cause, in some persons, cystinuria—these and many other questions concerning a "too much" of food or constituents of food the time prevents me from answering. But I hope that some of the gentlemen present,

[redacted] time to give further comments

[redacted] of all or certain constituents,
[redacted] underfeeding. I want, how-
[redacted] due to a so-called "partial"
[redacted] a food in which only one or
[redacted]
[redacted] deficiency of different sorts of salts
[redacted] too small quantities of lime pro-
[redacted] deficiency of lime seems also to cause a
[redacted] as well as of the electrical irritability of the
[redacted] authors maintain the opinion that
[redacted] to some extent, the spasmophilia of
[redacted] pointed out that a prolonged feeding
[redacted] an anemia due to the milk's contain-
[redacted] How can we live without albuminous sub-
[redacted] of their assimilation. I beg also to recall
[redacted] Willcock and Hopkins, showing that mice living
[redacted] of carbohydrates, fat, and salts), died much
[redacted] tryptophan was added to their food.
[redacted] does not contain a certain amount of carbo-
[redacted] of the fats becomes deficient, causing the
[redacted] and an "acidosis."

[redacted] however, I want to draw attention to the "partial"
[redacted] causing beriberi and scurvy. The reason is, in the first
[redacted] these two diseases are the maladies I know from personal
[redacted] In the second place, several facts concerning just these
[redacted] show in a most pregnant way, that our scientific knowledge
[redacted] in relation to disease, as well as to health, is, at present, rather
[redacted].

I beg to start with the following introductory remarks:

As for beriberi. Eijkman has stated that chickens become para-
lysed and die with a polyneuritis when fed on rice groats ("polished
rice" only: but they do not get ill when small quantities of rice bran
"polishings of rice") are added to the groats. Polyneuritis being
also the characteristic symptom of human beriberi, Dr. Vorderman
examined the prisons of Java, and stated beriberi to be frequent when
the prisoners ate rice groats as their staple diet, and, vice versa,
where the groats contained rice bran the disease was very seldom
observed. Later on, Grijns has found, in Java, that pigeons, too,
get polyneuritis when fed on rice groats only, and that the beans
that the Malays call Katjang hidjoe (phaseolus radiatus) have the
same preventive influence on the polyneuritis of poultry as rice bran.
Basing their work on these observations, Kiewit de Jonge and Huls-
hoff Pol have proved, by means of extensive experiments on man,

that these beans also prevent and cure human beriberi. In the meantime, Braddon had observed that the Tamils, a tribe in India, do not get beriberi as long as they use their own rice. This so-called "cured" ("parboiled") rice is prepared in such a way that it contains much bran. Therefore, "cured rice" has been introduced, to a large extent, in India and the Philippines, and has been proved to be of the greatest benefit as a preventive as well as a curative remedy against this scourge of the tropical countries. (Ellis, Fletcher, Fraser and Stanton, Heiser.) The same applies to a simple addition of rice bran to ordinary rice groats (French Cochin China).

These researches have been proved, by means of experiments on poultry, to be due to some hitherto not defined nutritive constituents being wanting or not present in sufficient quantities in the rice groats (that is, the inner layers of the grain), while they are contained in the bran (that is, the outer layers of the grain). They can be extracted by means of water (Eijkman), or neutral (Eijkman), or acid alcohol (Fraser and Stanton, Shiga and Kusama), and prevent the disease, not only when given in the food, but also subcutaneously (Eijkman). Basing his statement on extensive and suggestive experiments, Schaumann has started the idea that these constituents represent compounds of phosphorus; however, Eijkman, Fraser and Stanton, and Funck have come to different conclusions.

As for scurvy, this disease has been studied by experiments on animals at the Hygienic Institute of the University of Christiania. When fed on a one-sided diet consisting of bread, groats, or grains only, guinea pigs always die, mostly after about four weeks. They always show loose teeth, and often, but not always, hyperemic gums. In about 80 per cent of the animals there appear hemorrhages; in accordance with certain reports on infantile scurvy (for instance, Barlow's) they appear rather seldom in the skin, but mostly round the knee joints and the foremost ends of the ribs at their connections with the cartilages. These latter hemorrhages are characteristic of human scurvy, in infants as well as in adults. There appear, further, in the majority of cases, so-called separations of the epiphyses of the tubular bones, that is, fractures at the epiphyseal ends of their shafts. These separations, too, are characteristic of scurvy in man as long as the ossification is not yet finished. Finally, the animals show almost constantly the peculiar microscopical changes of the bone system which are specific to human scurvy.

That is, at the foremost ends of the ribs, at their connections with the cartilages, and at the ends of the shafts of the tubular bones, just beneath the intermediate cartilages, the normal, closely packed lymphoid cells of the bone marrow disappear and are substituted by a fibrillated or reticular tissue which is poor in cells and often

contains hemorrhages. However, the identity of this experimental disease with human scurvy is not limited to the pathological anatomy only; the same applies to its etiology. Apart from other facts mentioned below, human scurvy, too—in infants as well as in adults—has often been seen to be produced by a prolonged one-sided diet consisting of farinaceous nutriments only (siege of Paris; famines in Russia; failures of the potato crop in the northern part of Norway; Barlow's observations on the appearance of infantile scurvy after a prolonged feeding on different sorts of patented farinaceous infants' foods; a one-sided feeding with the latter produces also the experimental disease). On the other hand, the "antiscorbutic" vegetables, preventing and curing human scurvy, do also prevent and cure the experimental disease. I may also add that lime juice, having so great a reputation as a human antiscorbutic, also influences the experimental disease in a markedly favorable way. Finally, pigs, too, get experimental and typical scurvy when fed on rye bread only.

This disease, too, has to be explained by some nutriments containing or not containing sufficient quantities of peculiar constituents being present in other articles of food. We have, in Christiania, been able to extract them by boiling freshly dried cabbage with a solution of one-half per cent citric acid in water. Not as good, but still of a pronounced preventive influence, are extracts prepared by acid alcohol. As for the nature of these substances, however, we are, at present, only able to tell that there must exist more than one of them. This will be evident from different facts mentioned below.

Taking these two diseases as my starting point, I shall try to show how different sorts of diet possess—or not unlikely may possess—injurious or beneficial qualities that we are not accustomed to imagine and which not seldom are of an astonishing and at present unexplainable character.

1. *Grains, groats, flour, dried beans, and peas*, when of good quality, we do not, as a rule, consider as sources of disease. Nevertheless we ought not to let them pass without closer observation.

Starting with the criterion of the diet causing beriberi—that is, the polyneuritis of poultry—no sorts of unmilled grains examined have been able to produce this disease. The same has been found to apply to oaten groats and flour, as well as to rye flour. On the other hand, apart from rice groats, also barley groats and flour, when given as the only nutriment, provoke it; and—what is rather astonishing—the same applies to wheat flour. As for preventive articles of food we have seen that the phaseolus radiatus beans prevent (and cure), not only the experimental disease, but also human beriberi. Further experiments (in Christiania) have shown

that ordinary dried peas, as used on board of ships, prevent the experimental disease exactly as well as phaseolus radiatus. However, this does not apply to the Javanese Soya beans (soya hispida tumida Java); and still they contain about twice as much albuminous substances, seven times as much fats, and 37 per cent as much ashes as phaseolus radiatus (Grijns).

These facts are also of interest when studying the so-called ship-beriberi on board Norwegian ships. Till 1894, Norwegian sailors ate, on long voyages, rye biscuits, and got almost daily, or four to five times a week, peas and salt meat for dinner. In order to spare the teeth of the sailors, and make the food less monotonous, there was introduced, in 1894, a new scale of diet. After this time, the sailors have baked soft bread on board, using wheat flour or a mixture of wheat and rye flour, in proportions 1:1 or 2:1; at the same time, peas have only been used once or twice a week. (For a substitution of salt by tinned meat, see below.) But the results did not prove equal to the expectations. Because, till 1894, Norwegian ships have been practically free from beriberi; after this year, however, they have suffered very heavily from it. This accident coincides with the fact that not only wheat flour, but also the said mixture of rye and wheat flour (but not pure rye flour) produces polyneuritis of poultry, and vice versa: that the reduction of the peas reduced the quantity of a preventive remedy against this disease.

Contrary to these results, however, all sort of grains, groats and bread produce, when used as a one-sided diet, experimental scurvy. As far as wheat and rye bread is concerned, this applies also to scurvy in man. (Siege of Paris; northern Norway.) However, in order to produce the latter disease, a one-sided diet consisting of bread must be continued for months. This is the reason why the short "water-and-bread" penalty of our days does not provoke scurvy; in former days it lasted sometimes for months, and scorbutic cases were frequent. Most surprisingly, also, a one-sided diet, consisting of rice groats continued for months, has been observed to provoke human scurvy (Siege of Paris; very likely the patients also suffered from symptoms of beriberi; but this is not mentioned in the reports). I may add, that a one-sided food, consisting of rice groats only, also produces scurvy in guinea pigs. As for peas, they prevent neither the experimental nor the human scurvy. With respect to beans, I have no information.

2. FRESH VEGETABLES AND FRUITS.

As for beriberi, I limit myself to mentioning that fresh vegetables have a marked, though not always satisfactory, curative and preventive effect on ship beriberi. Fresh carrots and cabbage prevent also the polyneuritis of poultry, but only in comparatively large

quantities. Very likely this may explain why Hulshoff Pol has not obtained satisfactory results when experimenting with vegetables on cases of human beriberi.

As far as human scurvy is concerned, it is an old observation that fresh, raw or boiled, succulent vegetables are antiscorbutics, and that this quality is most pronounced when they are raw. Though less known, it is also an old tradition that the preventive influence of some fresh fruits is markedly best when they are unripe; with regard to the fruits of the so-called guava, the correctness of this tradition has been proved, in the 18th century, by direct experiments on man (Trotter, medic. nautica). However, when considering the experimental scurvy of guinea pigs, we meet with a good many other astonishing facts. For instance, if the fresh leaves of cabbage are boiled for 1 hour at 100° C., they lose some, but not much, of their pronounced antiscorbutic qualities. These qualities belong also to the unboiled, freshly pressed and filtered juice of cabbage; and still the juice loses most of its preventive power when heated for 10 minutes at 60° C. Again, the freshly pressed and equally anticorbutic juice of sorrel resists a boiling for 10 minutes at 100° C. This juice is markedly acid, and if a small quantity of citric acid is added to the juice of cabbage, this juice, too, acquires the same resistance. On the other hand, these acid juices lose their antiscorbutic qualities when kept, for some months, in closed bottles. However, contrary to this result, lime juice apparently can be kept for any time without losing its preventive properties.

How far we are from an extensive knowledge of the influence of the vegetable kingdom on health also appears from the following facts. In the old times several expeditions suffering from scurvy recovered by using a decoction of fresh pine needles. This decoction has also a markedly favorable influence on the scurvy of guinea pigs. Who taught these old expeditions to do so? Who taught Cartier, on his second voyage to Newfoundland in 1535, to use this remedy with the greatest benefit, when only three of his 110 men were left sound from scurvy?

3. FRESH ANIMAL NUTRIMENTS.

When added to rice groats, fresh meat boiled at 100° C. does not protect against the polyneuritis of poultry, though it prolongs the disease (Eijkman). Neither does it prevent human beriberi, as far as we can judge from ship beriberi, and the same applies to human scurvy when meat is not used as the only nutriment. However, some old North American Indian tribes have used meat as their only nutriment without getting scurvy.[1] The same is said to apply to the old North American trappers [1] and to the Samojeds.

As for fresh cow's milk, its influence on beriberi, or polyneuritis of poultry, is not yet known. However, it prevents infantile scurvy when raw, but does not when heated to 70° C. or more. Exactly the same applies to the influence of raw and heated milk on experimental scurvy (Fröhlich).

Proceeding to some other animal nutriments, once more we meet with some strange phenomena. For instance, the yolk of eggs protects against the polyneuritis of poultry, while the effect of the white of eggs is very uncertain (Eijkman). And when the Eskimos are afflicted by scurvy their best remedy is not sorrel, or scurvy grass, etc. As soon as they use the fresh liver of seals, and, above all, so-called fresh "matak," that is, the rete Malpighi of the skin of whales, they recover rapidly (Bertelsen and others)—a most extraordinary remedy.

4. PRESERVED FOODS.

When the tinning of meat was invented, it seemed to mark an important progress. When prepared carefully such meat is sterile and protected against decomposition; at the same time, when examined by means of the usual chemical tests, it appears to be as wholesome as fresh meat.

However, when examined by means of biological methods, it turns out differently. In the factories tinned meat is boiled for about one hour at 120° C. However, if fed on such meat only, but not on meat boiled for the same time at 100° C., chickens die from the same polyneuritis as when fed on rice groats. Even when boiled for one-half hour at 110° C. the meat produces the disease (Grijns, the author). This latter "steam boiling" is used for cooking in many hospitals and is, therefore, open to criticism. I may also add that Norwegian sailors did not use tinned meat till 1894. After that year, however—that is, when ship beriberi became frequent on board Norwegian ships—they have used it two to four times a week.

As for scurvy, a heating for one-half hour at 110° C. markedly reduces, and a heating for one hour at 120° C. destroys most of the preventive influence of cabbage on the scurvy of guinea pigs. However, here again we meet with a strange fact, since the juice of raspberries can be boiled for one hour at 110° C. without losing any of its highly preventing influence on the scurvy of guinea pigs.

Preserving by drying.—At the beginning of the eighteenth century the Hungarian physicians tried to meet a severe outbreak of scurvy with dried vegetables sent from the college of physicians at Vienna (Budd, in Tweedie's library of medicine). But the experiment failed completely. Nor did dried potatoes and other dried vegetables prevent scurvy in the North American War of the Rebellion.[2]

In spite of these observations, it is a widespread belief that dried vegetables are as wholesome as fresh ones as soon as they are carefully dried and protected against decomposition. However, it is easy to show the reports mentioned to be correct, by feeding guinea pigs on a mixture of some sorts of farinaceous food and dried cabbage, potatoes, dandelion, or carrots.

As for polyneuritis of poultry and tropical beriberi, corresponding observations are lacking. As a rule, however, ship beriberi breaks out, on board Norwegian ships, when the sailors have eaten, for some time, dried potatoes; on the other hand, experience shows that the crews recover as soon as they get fresh ones (for instance, from a passing vessel).

5. FERMENTED BEVERAGES.

Though wheat bread always produces polyneuritis in pigeons, the disease often appears much later when the bread is baked with yeast than if baked with baking powder (the author). Again, Schaumann has shown that pigeons about to die from a feeding on rice groats recover, as if under the influence of a magic power, when getting a small quantity of yeast. As for human scurvy, this disease, too, has repeatedly been observed to be cured by ordinary yeast.

Therefore, very likely the same applies to beverages fermented by means of yeast, and containing the products of its metabolism. This corresponds also with several old reports pointing out that wine and beer (but not distilled alcohol) has a markedly, but not always satisfactorily favorable influence on scurvy. Beer also seems to be able to prevent ship beriberi. Under these circumstances, it may be that the extensive use of fermented beverages of former days, at least in some periods and in some climates, when the antiscorbutic nutriments were scarce or wanting, has been due to a rational instinct.

On the whole, our present knowledge of the diet in relation to beriberi and scurvy shows that, in our daily food, and, above all, in the vegetables nutriments, there are mysterious forces at work, the outlines of which are only just beginning to appear. How mysterious they are will finally be evident from the following experiment: When fed on oats or barley only, guinea pigs constantly die from scurvy; but if we moisten the grains and make them sprout—that is, when we convert them into fresh vegetables—they prevent the disease (Fürst). How is this to be explained? What forces have been in action, and what unknown chemical processes have taken place?

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[1] See the medical and surgical history of the War of the Rebellion, Washington, 1888, pt. 3, vol. 1, p. 714.

[2] See the work mentioned, pp. 703 and 710.

DER EINFLUSS DER BEREITUNG DER NAHRUNGSMITTEL AUF IHREN NÄHRWERT.

Dr. MAX RUBNER, Profesor of Physiology and Director of the Physiological Institute, Berlin, Germany.

Die Zubereitungsweise der Nahrungsmittel ist Sache des Kochkunst in weitesten Sinne des Wortes eine echt menschliche Kunst. Ihre Folgen für den Nährwert der Kost des Menschen darzulegen wäre eine recht dankbare Aufgabe, deren Lösung aber doch nicht ganz einfach ist. Wenn ich Ihnen all das mitteilen sollte was auf diesem Gebiete von Bedeutung ist, so müsste ich Ihre Zeit ganz über Gebühr in Anspruch nehmen, ich würde aber den Beweis erbringen können, dass die Kunst des Kochens, die in mancher Richtung recht zurückgegangen ist, auch eine wissenschaftliche Grundlage besitzt und manche Fragen einschliesst, die an physikalisch chemische physiologische Kenntnisse ziemliche Anforderungen stellt. Ich werde mich bei der Kürze der Zeit nur auf einige kurze Gesichtspunkte beschränken müssen, umsomehr als bei einem internationalen Kongress vielleicht jede Nation sonst ein Anrecht hätte, von ihrer eigenen Kochweise etwas zu erfahren.

Die noch empirische Kochkunst erreicht den Zweck, dass sie eine Fülle von Nahrungsmitteln, die an sich für die Menschen unbrauchbar oder ungesund sind, in eine brauchbare, geniessbare gesunde Form überführt, und andere an sich geniessbare in bessere verfeinerte Speisen umformt.

Die Bewertung der Nahrungsmittel und Speisen erfolgt nach sehr verschiedenen Gesichtspunkten.

Unter Nährwert, im engsten Sinne, und vom wissenschaftlichen Standpunkt aus, verstehen wir den Gehalt an solchen Stoffen, welche dem Körper für seinen stofflichen und energetischen Bedarf zugute kommen können. Diese Begriffsbildung ist also nicht chemischer Natur, sondern physiologischer Natur, denn sie setzt voraus, dass wie auch die Verdauungsfähigkeit der Speisen mit in Betracht ziehen. Die Nahrungsmittel und Speisen lassen sich in dieser Hinsicht experimentell prüfen und untersuchen.

Die öffentliche Preisbildung weiss natürlich von diesen Dingen nicht viel oder garnichts; sie bewertet die Nahrungsmittel nach ganz anderen Gesichtspunkten, vielfach nach dem, was die Küche aus derselben machen kann und nach gewissen allgemeinen Anschauungen. Diese Preise sind zum Teil absolut imaginär. Wenn jemand im Sommer für Erdbeeren wenige Pfennige, und in Februar das mehrhundertfache dieses Preises bezahlt, so ist das eben ein Liebhaberwert, wer den Kaviar liebt, bezahlt unendlich, 30 mal mehr als für das gleiche Gewicht Hühnereier, u. s. w. Wenn man einstmals Gold für Speisen aus Vogelzungen u. dgl. hingegeben hat, so sind

das Dinge, über die wir heute lächeln. Ich möchte aber in meinem Urteil doch etwas zurückhalten, weil ich die Geschmackswerte nicht nach jeder Richtung als etwas Nebensächliches halte, weil man zu leicht in einer Spezialbetrachtung zu einem Punkte kommt, wo es heisst: De gustibus non est disputandum.

So zwecklos sich also auch der Preisgeldwert, in seinen Auswüchsen ansieht, ist er es aber doch nicht, wenn man nach den Verhältnissen des einfachen rationellen Haushaltes ihn betrachtet; es ist doch etwas mehr Methode darin. Man bezahlt allerdings auch da nicht den Gehalt an Nährstoffen, wohl aber gewisse Eigenschaften der Nahrungsmittel die wir die Genussmitteleigenschaften nennen können, weil sich in ihnen gewisse Eigentümlichkeiten der Nahrungsmittel, die zu einer, wenn auch bescheidenen Anregung des Geschmackes führen, mit verbunden sind; oder gewisse allgemeine Vorzüge zum Ausdruck kommen. Praktische Ernährung kann man nicht mit Nahrungsstoffen allein betreiben, sondern man muss auch diese etwas schwieriger zu fassenden Genussmitteleigenschaften mit heranziehen. Gerade die Zubereitung der Kost arbeitet auf eine Veredlung der Speisen in dieser Hinsicht hin.

Der Geschmackswert verschafft uns nicht allein das Gefühl der Befriedigung, ohne welche ein bekömmliches Essen nicht zu denken ist, es ist uns auch der Indikator für die richtige Beschaffenheit der Speisen, und eine Gewähr für bestimmte Wirkungen, für die glatte, ungestörte Verdauung, für einen normalen Verlauf der Darmfunktionen und ähnliches. Für die breiten Schichten des Volkes ist es mehr Ahnung als Wissen, aber wir sind durchaus in der Lage, bei vielen Kochprozessen, bei denen anscheinend nur eine Geschmacksänderung auftritt, wirkliche Rückwirkungen auf den Magen und Darm nachzuweisen.

Die äusseren Eigenschaften, auch Geruch und Geschmack, sind die Wächter der Gesundheit; aus dem Gesamteindruck schliessen wir auf die Güte der Ware und danach bezahlen wir auch den Preis.

Die Zubereitung der Kost muss auf diese beiden Seiten der Probleme also gebührende Rücksicht nehmen, denn die erstere schafft vielfach erst einen Nährwert, weil sie die Nahrung in jene Form bringt, in welcher sie vom Menschen als Nahrungsmittel anerkannt wird.

Die Bedeutung der Zubereitung wollen wir unter verschiedene grössere Gesichtspunkte zu bringen versuchen. Ein wichtiger Teil ist die Vorbereitung der rohen Nahrungsmittel.

Von einer rationellen Küche verlangen wir in sanitärer Hinsicht vorbereitende Aktionen, welche den Zweck haben, die Nahrungsmittel zu reinigen, wie z. B. das Abspülen der rohen Früchte oder anderweitiger roh verzehrter Materialien (Salate, Brunnenkresse). Hierher gehört auch die Beseitigung der Unreinheit aus der Milch durch Fil-

tration in den Centralmolkereien. Bei all diesen Manipulationen ist der Verlust an Nährwerten absolut belanglos.

Die Speise muss in ihrem ganzen äussern Gewähr für die Reinlichkeit der Zubereitung bieten.

Das Gefühl der Reinlichkeit der Zubereitung ist für den Kulturmenschen und hygienisch denkenden Menschen das allererste Erfordernis einer guten Nahrung. Das bekannte Haar in der Suppe kann allein schon jeden Genuss an der Mahlzeit verberden.

Zu den vorbereitenden Operationen gehört die Entfernung minderwertiger Teile namentlich bei Vegetabilien und Obst. Die Reinigung der Oberfläche durch Schälen und Schaben, Beseitigung von Schalen wie bei den Hülsenfrüchten, grob verholzter Teile des Salates.

Ebenso ist es zweckmässig mit Schalen und Kernen bei Früchten den Darm nicht zu belasten, da abgesehen von anderen Gefahren ein nachteiliger rascherer Durchtritt der Speisen durch den Darm eingeleitet wird, damit Verlust von Nahrstoffen verbunden ist.

Das Klopfen und Schlagen des Fleisches verfolgt den Zweck, durch innere Zerreissung der Zellen und Gewebe die Kauarbeit zu erleichtern, das Gleiche wird erreicht beim Zerkleinern des Fleisches durch Hacken. Auch bei Vegetabilien, wie beim Spinat, dem Kehl u. s. w. wird die Zerkleinerung vorgenommen, wodurch meist die Verwertung der Kost wirklich erhöht wird, weil die Zellen die an sich für den Verdauungssaft nicht durchgängig sind, gesprengt werden.

Die mechanische Zerkleinerung ist aber da zu unterlassen, wo sie den Kauakt unnötigerweise ausschaltet, denn dieser ist notwendig, weil er einerseits durch Auslaugung der Nahrung durch den Speichel die schmeckenden Extraktivstoffe, die Geschmacksbefriedigung erhöht, die Anregung der auch anderer Verdaungssäfte begünstigt und bei Vegetabilien bereits im Munde die Verdauung einleitet. Nur gröblich zerkleinertes Material wird in toto hinuntergeschlungen und kann die Magenverdauung stören und verlangsamen.

Wohl die wichtigste Zubereitungsmethode der Nahrung ist die Anwendung der Wärme.

Die letztere erhöht an sich die Verdunstung der Geschmacksstoffe und übt dadurch eine anregende Wirkung auf den Verdauungsapparat aus, die warme Speise gibt auch vom Magen aus ein Gefühl der Behaglichkeit. Fette werden durch die Wärme geschmolzen, was auf die Ausnützung derselben im Darmkanal zurückwirkt. Erstarrte Fette erzeugen im Munde eine Herabsetzung des Tastgefühls und der Geschmackswirkung.

Die wichtigste sanitäre Bedeutung des Erhitzens der Speisen liegt in der Abtötung von Mikroben und Parasiten. Zwei wichtige Vorgänge sind zu nennen. Die Pasteurisierung, welche bei 70°–75° ausgeführt; meist den Geschmack der rohen Nahrungsmittel unverän-

dert lässt und nur die vegetativen Formen der Mikroben vernichtet, und die Sterilisierung, welche vollkommene Abtötung der Mikroben erzielt. Neben diesem Gesundheitsschutz gehen durch die Wärme aber noch andere wichtige Veränderungen der chemischen Beschaffenheit vor sich. Es wird am besten sein, wenn ich diese nach Nahrungsmitteln getrennt behandle.

Muskelfleisch und Organteile gewinnen etwa um 70° Wärme den spezifischen Geruch und Geschmack der Bouillon bis 100° steigert sich derselbe, geht dann bis 120° in den Bratengeruch über, endlich riecht das Fleisch unangenehm und brenzlich. Die Eiweissstoffe gerinnen zum grössten Teil; bei 50° ist schon mehr als die Hälfte, bei 70° schon 9/10 bei 80 Prozent das gesamte gerinnbare Eiweiss geronnen (Milroy). Dabei ändert das Fleisch das Volumen nach Ferrati zwischen 15–45° um 3.6 Prozent; zwischen 45–56° um 7.21 Prozent; zwischen 56–66° um 15.83 Prozent; zwischen 66–76° um 10.85 Prozent; zwischen 76–86° um 8.30 Prozent; zwischen 86–96° um 1.73 Prozent.

Diejenigen Gerinnungen welche die stärkste Kontraktion verursachen, liegen zwischen 60 und 70°. Erhitzt man das Fleisch noch höher als 100° so nimmt es noch weiterhin an Volumen ab und wird fortwährend zäher.

Diese Volumenänderungen treten immer ein wie auch die Art der Ernährung vorgenommen werden mag.

Beim Kochen erleidet das Fleisch nur eine Temperaturerhöhung auf 100° ebenso beim Dünsten, oder Einlegen in Saucen.

Beim Braten erreicht die Temperatur an der Aussenseite des Fleisches 120° und darüber, bei dem Rösten, wobei Fett zugesetzt wird, 150–160° hierbei verliert das Fleisch Wasser durch Verdunstung, worauf das Fett die Fasern innig durchtränkt, bei 220° zerlegt sich das Fett.

Die Volumenverminderung des Fleisches erfolgt hauptsächlich in der Längsrichtung der Faser, wobei vor allem der Fleischextrakt und etwas Eiweiss und Leim und Salze aus dem Fleische austreten. Beim Kochen in Wasser geben sie die Fleischbrühe deren Menge beim Erwärmen grösserer Fleischstücke nur sehr unbedeutend durch Auslaugung von Extrakt aus den oberflächlichen Schichten vermehrt wird. Beim Braten trocknet bei der hohen Trockenheit der Luft des Bratrohres ein Teil des Extrakts an der Oberfläche des Fleisches und gibt die Kruste, ein Teil fliesst ab und bildet die Sauce.

Beim Dünsten des Fleisches in Dampf von 100° erfolgen ähnliche Vorgänge wie beim Kochen, nur findet keine Auslaugung der oberflächlichen Schichten statt auch keine Konzentration des Saftes durch Verdunstung.

Todtenstarres Fleisch schrumpft stärker wie ganz frisches. Fischfleischsorten ziehen sich weniger zusammen wie Fleisch von Säugern, bleiben also wasserhaltiger. Von den Organen von Säu-

gern verändern Leber, Niere und Gehirn beim Erhitzen ihr Volumen weniger als Fleisch, am wenigsten die Lunge, weil der austretende Saft in den Alveolen und seinen Bronchien genügend Raum zur Ablagerung findet.

Das Eindringen der Wärme in das Fleisch ist natürlich abhängig von den Temperaturdifferenzen, der relativen Oberfläche, dem Leitungsvermögen; all das ist wandelbar, das Leitungsvermögen kann schon bei frischem Fleisch sehr different sein, wegen des ungleichen Fettgehalts, während der Erwärmung nimmt das Leistungsvermögen durch die Schrumpfung ab, weil das Fleisch wässrige Flüssigkeit verliert und eiweiss- und fettreicher wird, die Wärme dringt aber andererseits rascher ein, weil durch die Schrumpfung die Leitungsstrecke für die Wärme geringer wird. Der wichtigste Faktor für die Geschwindigkeit der Erhitzung bleibt immer die Grösse des Fleischstückes ein Würfel von 6 C. Seitenlänge erreicht in 2,580 Sekunden 100° in der Mitte, ein solcher von 11 C. erst nach 8,550 Sekunden und beim Erhitzen auf 70° ist nur $\frac{1}{3}$–$\frac{1}{2}$ soviel Zeit nötig als beim Erwärmen auf 100°.

Die Bedeutung dieser Zubereitung des Fleisches für den Nährwert ist folgende:

Der Geschmackswert steigert sich ausserordentlich, die Extraktivstoffe regen die Verdauung erheblich an. Das Nahrungsmittel ist im erhitzten Zustand dichter und gehaltvoller als vorher. Durch die Gerinnung des Eiweisses wird zwar das Eiweiss etwas widerstandsfähiger beim Kauen aber andererseits das im rohen Zustande sehr zähe Bindegewebe gelöst. Die Härte durch Eiweissgerinnung nimmt zu, wenn das Fleisch höhere Temperaturen als 70° annimmt.

Besonders die hohen Temperaturen und längere Anwendung der Wärme führen dazu, dass das Bindegewebe sich ganz auflöst die Fleischsubstanz aber als derbfaserige Masse zusammenhält. Derartiges Fleisch findet sich unter den Büchsenkonserven häufig. Die Folge ist, dass sich beim Essen sehr schnell der Fleischsaft abtrennt und geschluckt wird, während die Fasern schwer zu zerkleinern und geschmacklos ist. Die Verwertung solcher Konserven für längeren ununterbrochenen Gebrauch für die Armeeernährung hat sich aus dem Grunde nicht bewährt, weil die feste faserige Masse des Fleisches nach mehreren Wochen dauernden Genusses unangenehm empfunden wird.

Jeder übermässige Widerstand beim Kauen führt zu ungenügender Zerkleinerung, zum Verschlucken grösserer Brocken die sich langsamer im Magensaft auflösen, und Beschwerden hervorrufen können.

Je mehr Fleisch von Fett durchtränkt ist, desto schwerer wird es vom Magensaft gelöst; der natürliche Fettgehalt nimmt prozentisch bei jeder Einwirkung der Wärme zu. Wird aber zugleich, wie in der Bratenkruste oder beim Rösten auch noch Wasser durch Verdunstung

verloren, und die Fleischfaser ganz von Fett durchzogen, so können solche Teile ganz unverdaulich werden und in den Fäces unverändert austreten, nachdem sie vorher Magendrücken und ähnliches hervorgerufen haben.

Das Einlegen von Fleisch in Salzlösungen zur Bereitung von Pökelfleisch oder Schinken vermindert stets den Nährwert insofern, als schon mit der Salzlake viel phosphorsaure Salze und Fleischextrakt verloren geht und ein weiteres Ausziehen noch ausserdem, wenn die Erhitzung dieser Fleischsorten eintritt, während beim Kochen und Braten gewöhnlichen Fleisches die austretenden Substanzen in die Sauce oder die Bouillon übergehen, und hierin verzehrt werden.

Fleisch, das längere Zeit der Autolyse überlassen wird, wird weicher, wahrscheinlich nicht nur wegen Veränderung und teilweiser Lösung des Zellinhaltes der dann beim Erhitzen feinfleckiger gerinnt, sondern auch wegen der Auflösung von Bindegewebe. Bei dem nach Wildart zubereiteten Fleische kommt wahrscheinlich eine Wirkung peptonisierender Bakterien in Frage. Beim Einlegen in Essig kann das Fleisch ebenso weich werden, wie nach Autolyse. Das Bindegewebe quillt und wahrscheinlich entsteht etwas Acidalbuminat, das nachträglich beim Erhitzen nicht mehr gerinnt.

Die Zubereitungsweisen des Fleisches laufen alle darauf hinaus, teils eine Mehrung des Genussmittelwertes durch die Bildung riechender und schmeckender Produkte, deren Wirkung auf die Verdauungsorgane durch Pawlow näher verfolgt worden ist, zu erreichen, und die störenden Grade der Zähigkeit zu mindern.

Ein Unterschied in der Ausnützung wird bei normalen Verdauungsorganen zwischen rohem und erhitzten Fleisch nicht gefunden. Der Darm des Menschen arbeitet was die Fleischausnützung anlagt, ebensogut wie der der Fleischfresser, aber der Verlauf des Verdauungsprozesses ist um so angenehmer und besser, je weniger zäh das Fleisch ist und je besser es sich kauen lässt.

Der Wert der Extraktivstoffe aus Fleisch verschiedener Herkunft ist sehr verschieden. Fleisch junger Tiere ist in dieser Hinsicht minderwertiger und verträgt besser das Braten. Die beste Fleischbrühe liefert Rindfleisch und älteres Geflügel. Fischfleisch ist überhaupt arm an wirksamen Extraktivstoffen, hat also einen geringen Küchenwert, auch bleibt es wasserhaltiger beim Kochen. Das Backen in Fett bei recht hoher Temperatur ist daher zur Erhöhung des Geschmackes hier sehr beliebt. Die Kruste besteht aber nicht aus Röstprodukten des Fisches, sondern aus jenen des aus Mehl, Ei und Fett gemengten Teiges.

Bei getrockneten Fischen wurde die Resorption etwas herabgesetzt gefunden.

Die Milch kommt entweder in rohem, pasteurisierten oder sterilisiertem Zustande zur Anwendung. Bemerkenswert ist, dass manche

Kinder nur rohe und keine vorher erwärmte Milch vertragen, sondern an Barlowscher Krankheit erkranken, und zu Grunde gehen können. Die Pasteurisierung für die Milchversorgung grosser Städte ist nicht zu empfehlen, da sie die Kontrolle, ob die Milch noch frisch ist oder nicht, erschwert. Durch die Erhitzung auf 70–100° fällt Lactalbumin aus, die Spuren von Caseingerinnung sind ohne Belang.

Bei Erwärmung über 100° wird die Milch durch Zuckerzersetzung braun und das Fett, z. T. aus dem Emulsionszustand in grössere Fetttropfen übergeführt. Solche Milch soll zur Säuglingsernährung nicht verwendet werden. Zwischen gekochter und ungekochter Milch ist kein Unterschied in der Ausnützung, doch wirkt bei manchen Menschen rohe Milch auf eine Beschleunigung der Peristaltik ein. Die Milcheiweissstoffe werden im allgemeinen nicht so gut resorbiert wie die Fleischeiweissstoffe. Die einzelnen Menschen verhalten sich verschieden; bei manchen werden schon Mengen vom 4 Litern Milch pro Tag ganz unvollkommen bezüglich der Eiweisstoffe verwertet, andere ertragen bis 10 Liter täglich bei günstiger Ausnützung. Die Muttermilch wird von Kindern vortrefflich ausgenützt, die Kuhmilch etwas weniger gut. Die Ursache liegt in der grobklumpigen Gerinnung des Kuhcaseins. Ein Milch- und Käsegemenge wird weit besser resorbiert, weil der gekaute Käse die Abscheidung eines groben Kaseingerinnsels hindert. Sorgfältig mit Lab bei niedriger Temperatur feinfleckig geronnene Milch wird von Erwachsenen trefflich verwertet. Löst man Milchtrockenpräparate wieder in Wasser, so ist die Ausnützung eine ebenso gute wie für gelabte Milch oder Milch und Käse. Kefirmilch zeigt hinsichtlich der Resorption der Eiweissstoffe dieselben Verhältnisse wie gelabte Milch, hat aber noch vor den übrigen Milchpräparaten den Vorzug einer besseren Fettausnutzung. Es liefert die Kefirmilch genau die gleichen Verhältnisse der Resorption wie Milch und Käse.

Bei den Hühnereiern bringt die Gerinnung in der Wärme ein gleichmässiges Erstarren der Eiweissstoffe zustande, unter Abspaltung von etwas Schwefelwasserstoff aus dem Albumen. Es ist bekannt, dass die harten Eier, wenn sie nicht sorgfältig gekaut werden, leicht Magenbeschwerden hervorrufen. Das Ei ist der Infektion stark ausgesetzt, da die Eierschale für Bakterien permeabel ist, die Erhitzung der Eier vor dem Genuss ist also stets anzuraten. Das Ei gehört, auch wenn es hart gekocht genossen wird, zu den sehr gut ausnützbaren Nahrungsmitteln.

Die Vegetabilien werden zum Teil roh, zum Teil nach Behandlung durch die Hitze genossen.

Die wichtigsten technischen Ausführungen sind das Backen von Ceralien, das Kochen von Knollengewächsen, Leguminosen, Gemüsen,

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Stärke wirkt, beträchtlicher gemacht wird. Die Pflanzzellen werden durch das Erhitzen weichen, weil sie zum Teil gesprengt werden.

Teigwaren nehmen beim Kochen mehr Wasser auf und werden etwas kleisteriger wenn nicht durch etwas Eizusatz eine feste Bindung erfolgt. Reichlich ist die Wasseraufnahme auch bei den puddingartigen Speisen die Polenta und Risetto, noch grösser bei den Gemüsen. Die Puddings und die Gemüse erhalten je nach Volkssitte mehr oder weniger grosse Mengen von Fett zugesetzt.

Die starke Vermehrung des Volumens vieler vegetabilischen Speisen und das relative Sinken des Gehaltes an Nährstoffen ist ein nicht unwesentlicher Nachteil dieser Nahrungsmittel. Die Zeitdauer des Essens nimmt zu. Da das Kauen wie z. B. bei Teigwaren, vermindert ist und bei breiigen Substanzen ganz wegfällt, ist auch die Einspeichelung mangelhaft und die Geschmacksbefriedigung nicht selten ungenügend, würzende Zusätze unbedingt nötig.

Häufig findet sich bei Personen welche voluminöse Pflanzenkost geniessen eine starke Erweiterung des Magens. Das Sättigungsgefühl wird nur nach starker Füllung des Magens erreicht. Die animale und gemischte Kost sind wesentlich konzentrierter.

Im Allgemeinen steigt der Geschmackswert beim Erhitzen der Vegetabilien auf 100° nicht, obschon gekochte Speisen dieser Art eine gewisse Aenderung der schmeckenden und riechenden Stoffe erfahren. Anders, wenn die Temperatur von 100° wesentlich überschritten wird.

Besonders gut schmeckende Bestandteile werden durch das Rösten erzeugt. In ausgedehntem Masse geschieht dies beim Backprozess wo die von aussen den Teig treffende, strahlende Wärme von weit mehr als 100° diesen Prozess erzeugt. Aehnliches geschieht durch Einbringen von Teig in siedendes Fett, hier ist es die hohe Hitze des Fettes welche bei kurzer Berührung die Röstung vollzieht.

Bei Mehlspeisen, die in Gefässen erhitzt werden, vollzieht sich durch die strahlende Hitze der Wandungen des Backraumes an der Oberfläche die Bildung der wohlschmeckenden Kruste. All diese Speisen gelten daher als besonders wichtig, zur Abwechslung im vegetabilischen Menu. Ein nennenswerter Nährverlust entsteht dabei nicht.

Eigenartig ist die Herstellung poröser Gebäcke des Brotes. Die nötigen Mittel sind Hefe und Sauerteig z. B. chemische Mittel, welche Kohlensäuregas liefern. Die Gährungen geben besser schmeckende Produkte als die Blähung des Teiges durch Chemikalien. Hefe wird annähernd als Reinkultur verwendet, Sauerteig enthält immer viel säurebildende Bakterien. Hefegebäcke erzeugen meist feste, wenig saure Ausscheidungen; Sauerteig waren intensive Buttersäuregährung mit starker Gasentwicklung, stark sauren häufigen Kotentleerungen die schliesslich zu einer Einschränkung des Brotgenusses führen müssen.

Treten stark saure gasige Stühle auf, so ist die Ausnützung der Nährstoffe vermindert.

Von grösster Bedeutung ist es bei der Pflanzenkost verholzte Teile tunlichst schon vor der Nahrungsbereitung wo möglich zu entfernen. Der menschliche Darm ist auf eine Auflösung älterer Cellulose nicht eingerichtet.

Die unverdaulichen Teile gehen nicht nur ungenützt ab, sondern sie beschleunigen den Durchgang dieser Speisen durch den Darm, kürzen die Resorptionszeit, vermehren die Stühle, und bringen Nährstoffverluste.

Auch bei einer gut resorbirten Pflanzenkost ist die Menge des im Kot ausgeschiedenen N. erhöht, Pflanzeneiweiss völlig frei der Nahrung zugesetzt ist, soweit man dies von dem Klebereiweiss kennt, zwar weniger gut ausnützbar als jenes der Animalien, aber immerhin weit besser resorbierbar, als wenn es in natürlichen Nahrungsmitteln verabreicht wird.

Bei keinem Nahrungsmittel ist der Einfluss der Zubereitung so massgebend, wei bei den Ceralien. Wir kennen ihn genau aus zahlreichen Untersuchungen über Brot. Das Eiweiss der Körnerfrüchte liegt zum erheblichen Teil in Zellen eingeschlossen. Die Pflanzenzellen sind für die Verdauungssäfte der Menschen impermeabel das eingeschlossene Eiweiss kann also nicht verdaut werden. Völlig unzweckmässig ist nun die grobe Zerkleinerung des ganzen Getreidekerns, besser die Vermahlung nach Beseitigung der äusseren Hülle (Decortiortion) noch besser resorbierbar sind Hehle nach Entfernung der Kleie. Je vollkommener beim Vermahlungsprozess die Zellen gesprengt werden, desto resorbierbarer wird namentlich das Eiweiss gefunden.

Zahllose Patente und Mahlverfahren sind bereits angegeben worden, welche die Pflanzenzellen möglichst zerkleinern wollen, keine Zerkleinerungsweise kann aber die voluminöse Kotbildung natürlich ganz beseitigen, weil diese vom Cellulosegehalt abhängig ist.

Ob das Mehl verbacken oder zu Teigwaren verarbeitet wird, ist für die Verwertung anscheinend ganz gleichgültig.

Bei der Kartoffel ist zwischen dem Genuss gekochter oder als Salat oder als Brei genommenes Material kein Unterschied, wohl aber sieht man bei gerösteten Kartoffeln dass braune, ganz mit Fett durchsetzte Stücke unverdaut abgehen.

Ganz unverdaulich sind die Hüllen der Leguminosen, sie sind im Interesse einer guten Verwertung zu beseitigen.

Viele Vegetabilien erhalten einen reichlichen Zusatz von Fett, eine Benachteiligung der Fettresorption ist dabei nicht nachzuweisen, noch wird auch bei sehr grossen Fettmengen die Resorption der Vegetabilien gestört.

Zusatz von Käse, wie bei Polenta üblich ist, scheint die Resorption der Eiweissstoffe des Maises zu erhöhen. Es wird auch angegeben, das Fleischextraktivstoffe die Ausnützung einer vegetabilischen Kost begünstige.

Früchte werden zumeist in rohem Zustande genommen, da sie genügend Genussmitteleigenschaften besitzen. Das Zerkochen zu Brei bietet für halbreife Früchte sicher mitunter Vorteile gegenüber dem Genuss in rohem Zustande wenn etwa Stärke der unreifen Früchten vorhanden ist.

Früchte werden halbreif abgenommen und der Nachreifung unterzogen. Bei letzteren wird in der Regel eine Verminderung der Säure erzielt und die Bildung in Frutose. Genauere Kenntnisse über diese Gruppe von Nahrungsmitteln haben wir nicht, sie sind ja auch meist nur mit einigen Ausnahmen als Beigabe zur Kost bestimmt. Genauer sind nur die Bananen untersucht.

Die reife Banane verhält sich in der Ausnützung ähnlich wie manches Gemüse, gibt einen erheblichen Verlust an N-Material, während die Kohlehydrate gut aufgenommen werden. Die Banane steht im Ernährungswert des N wesentlich hinter der einheimischen Kartoffel zurück.

Die auf Jamaika hergestellten getrockneten Bananen erweisen sich namentlich bezüglich der Eiweissstoffe sehr ungünstig bei der Resorption, da diese bei reifen nur zu 54 Prozent bei getrockneten bis zu 80 Prozent zu Verlust gehen. Die getrocknete Banane erzeugt eine erhebliche saure Gährung im Darm, die ähnlich wie bei Schwarzbrot zu häufigen dünnen Stuhlentleerungen führt. Die unreife Banane ist hinsichtlich der Eiweissstoffe etwa so gut resorbierbar wie die reife Banane, der starke Gerbsäuregehalt aber lässt es zu einer Darmgährung nicht kommen, dagegen ist die in der unreifen Banane enthaltene rohe Stärke so gut wie unresorbierbar. Die unreifen Bananen müssen also vor dem Genuss erst gekocht oder geröstet werden.

Früchte werden, wegen ihres manchmal hohen Säuregrades mit Zuckerzusatz versehen, der Säuregrad ist ein Nachteil, der bei vielen Personen wesentliche Störungen der Magenverdauung herbeiführen kann, der Zuckerzusatz ist nur ein Geschmackscorrigens, hebt also die nachteilige Wirkung auf den Magen nicht auf.

Unter den schädlichen Wirkungen der Nahrungsmittel, sind die Darmgährungen, die ich erwähnt habe, sehr bedeutungsvoll. Bei animalischen Nahrungsmitteln haben wir die Fäulnis, welche aber selten zu stark entwickelten Uebelständen führt. Ein Teil des Nährmaterials geht zu Verlust indem die Darmbakterien sich entwickeln und ihre Leiber mit ausgeschieden werden; der Harn enthält dann Aetherschwefelsäure, auch Indigo findet sich in leicht bestimmbaren Mengen. Bei Fleisch- und Eiernahrung können also als solche charakteristische Typen für die Kotfäulnis dienen.

Bei Milch pflegt die Darmfäulnis wesentlich zurückzutreten. Bei Vegetabilien finden wir häufig eine völlige Aufhebung der Fäulnis dafür aber zunehmende Buttersäure Gährung und Gasbildung im Kot.

Mittel zu Einschränkungen der Buttersäurezersetzung sind bei Brot die Vermeidung des Sauerteiges. Neuerdings hat man versucht durch Beigabe von Bakterien zur Nahrung überhaupt die Gährung im Darm eine unschädliche Richtung zu geben, z. B. durch Milchsambacillen. Von aussen eingeführte Bakterien halten sich nicht lange gegenüber der üblichen Darmflora, es muss also stets für Wiederersatz der einzuführenden Bakterien gesorgt werden.

Die Bedeutung der Zubereitung der Speisen für die Erhöhung des Nährwertes ist noch keineswegs ausreichend untersucht, die angeführten Beispiele genügen aber, um auf die hohe Bedeutung dieser Frage hinzuweisen.

DIET AND METABOLISM IN FEVER.

WARREN COLEMAN, of Cornell University Medical College, New York City.

Empiricism has constituted the basis of the fever diet since the dawn of medical history.

While, on the basis of empiricism, the nutritive value of the fever diet has gradually been increased, reaching a maximum of some 2,500 calories toward the end of the nineteenth century, the value of the average diet has not exceeded, and has usually fallen below, that of 2 quarts of milk (1,400 calories a day).

The more liberal diets have not received the sanction of the profession at large, except in the treatment of tuberculosis and sepsis. Furthermore, the foodstuffs in the fever diets ordinarily employed have not been properly proportioned. The optimum proportions probably vary under different conditions, and data for the construction of the ideal fever diet are as yet incomplete, but the evidence which we possess indicates that undue emphasis has been placed upon the desirability of increasing the protein ration. Rubner recommended the liberal use of carbohydrate in fever on the ground of its low specific dynamic action; Lusk advised it because of its protein-sparing power, but these suggestions received scant attention from practitioners of medicine.

As has recently been proved for typhoid fever (and I believe it is equally true for other infective diseases), a diet furnishing 2,000 to 2,500 calories a day does not cover the needs of a patient with high fever.

Therefore it is evident that after 2,000 years of which we have record empiricism has proved a signal failure as the basis of the fever diet.

The ideal fever diet must be constructed upon carefully planned studies of metabolism in fever, controlled by equally careful clinical studies of the effects of different diets upon the patient. Valuable experiments have been carried out upon artificially infected animals (May, Weber, Stähelin), but I need scarcely remind this audience of the paucity of metabolism studies upon fever-stricken man.

THE INFLUENCE OF DIET UPON THE NITROGEN LOSSES IN FEVER.

The foundations for the scientific construction of the fever diet were laid by the early investigators, who discovered the loss of nitrogen in fever and who studied the ability of the fever patient to absorb his food.

The extent of the nitrogen losses in different fevers is comparatively well known. The influence of diet upon the losses has not, however, been the subject of such extended investigation. Yet notable experiments were made by Puritz and by von Leyden and Klemperer. Puritz's studies were confined to the effects of a high protein diet in typhoid fever; von Leyden and Klemperer investigated pneumonia as well as typhoid, employing high carbohydrate as well as high protein diets.

Puritz's diet consisted of 160 grams of protein, 60 to 90 grams of fat, and 300 grams of carbohydrate, and had an energy value of 2,396 to 2,677 calories a day. While he did not succeed in preventing the febrile loss of body protein, the clinical effects of this and similar diets, employed by Chudnowsky's pupils and others in Russia, were considered favorable.

Von Leyden and Klemperer's protein diet consisted of milk and peptone, and furnished from 1,000 to 2,000 calories a day; their carbohydrate diet consisted of milk, cream, lactose (200 grams), glucose (133 grams given subcutaneously), and sherry, with a maximum energy value of 3,300 calories a day. The fuel value of the carbohydrate diet was quite or nearly sufficient to cover the heat production of the average patient, judged by recent studies. With both types of diet they were able to reduce the nitrogen loss, but did not succeed in preventing it. Von Leyden and Klemperer concluded from their experiments that "the toxogenic destruction of tissue in acute fevers could not be prevented by means of food."

In 1907 Shaffer and Coleman undertook to reinvestigate the influence of diet upon protein metabolism in typhoid fever. Observations were made upon some 25 patients during two epidemics. The diet they used contained a moderate amount of protein and larger amounts of carbohydrate and fat than had heretofore been given to patients.

The most striking result of the investigation was that it was found possible in all cases to reduce the nitrogen loss to a minimum, and in some instances to bring the patient into nitrogen equilibrium.[1]

The amount of food required to accomplish this was very large—comparable only to that taken by persons performing arduous physical labor in cold climates, such as the lumbermen of the north woods—and, as will be pointed out later, was greater than the amount required to cover the heat production.

VARIATIONS IN THE TOTAL FOOD ADMINISTERED.

The amount of food required to reduce to a minimum, or prevent, the febrile loss of nitrogen varies with individuals and with the stage of the disease.

Individual variations.—The differences in the requirements of different individuals in the same stage of the disease (the febrile) are illustrated by the following cases [2] (in averages for periods):

	Number of days.	Range of maximum temperature.	Calories per kilogram.	N-intake.	N-balance.
Case 1	6	102.8–103.6	85	15	+0.6
Case 2	5	102.0–104.4	71	10.9	+0.9
Case 3	3	102.6–103.2	45	14	+1.2

These variations in requirement are probably dependent upon personal peculiarities of metabolism, such as are noted in health, and upon the differing intensities of the reaction of the hosts to the invading microorganism.

Variations corresponding to the stage of the disease.—The amount of food required varies also with the stage of the disease. To illustrate this the febrile period, convalescence, and relapses will be considered separately.

1. *The febrile period.*—Numerous studies have shown that the greatest loss of nitrogen occurs during this period. In Puritz's cases the loss diminished as the disease advanced, though the curve was broken from time to time by a sudden increase in the nitrogen output without a corresponding change in the condition of the patient. Cohn stated that the nitrogen excretion followed the temperature curve without paralleling it; in other words, that the nitrogen loss fell with the temperature. This probably occurs in many cases, but there is evidence to indicate that the loss may diminish with the advance of the disease, in cases of long duration, in spite of a continued high temperature. Grafe found that the longer the disease lasted the greater was the endeavor made by the organism to spare its protein. In one of our cases, to whom we were unable to give sufficient food, the urinary nitrogen fell from 22 grams on the twelfth, thirteenth, and fourteenth days, respectively, to 10 grams on the twenty-fourth, and 11 grams on the twenty-sixth days, though the temperature ranged higher. Throughout the duration of the febrile period, lasting some 60 days, the same tendency was exhibited.

From such observations it is apparent that the typhoid fever patient who is undernourished possesses the same ability to economize his resources, and especially to spare his protein, that is possessed by healthy persons who are starved or by those suffering from other wasting diseases.

According to Rubner, the economy of energy in chronically undernourished animals is only apparent; when the heat production is calculated upon the basis of weight, or surface area, it is found to be constant, or, in other words, the diminution in total heat production corresponds to the loss of weight.

Whether actual economy of energy occurs in the later stages of fever, when a patient is undernourished, has not been determined with certainty.

Patients who are liberally fed appear to exhibit no tendency to economy, as the following instances illustrate:

	Range of maximum temperature.	Calories per kilogram.	N-intake.	N-balance.
Case 1:				
Thirteenth to eighteenth days	102.8–103.6	85	15	+0.6
Twenty-third to thirtieth days	101.4–104.8	89	14.5	−2.1
Case 2:				
Ninth to sixteenth days	101.6–103.8	56	12.3	−4.9
Twenty-third to twenty-fifth days	99.8–100.2	39	16.1	−6.8

These cases apparently indicate that Rubner's opinion holds for patients suffering from typhoid fever as well as in starvation. They show also that the need for large quantities of food, judged from the standpoint of the nitrogen balance (there has been no reason to think that a delayed excretion of nitrogen modifies the balance) undergoes no material reduction until well on toward or into convalescence. We may conclude, therefore, that the amount of food required to reduce the nitrogen loss to a minimum or to prevent it continues undiminished throughout the greater part of, perhaps the whole, febrile period.

2. *Convalescence.*—The ability of the body to repair the damage wrought by the infective fevers is nowhere better shown than in convalescence from typhoid fever. The amount of food required to establish or maintain nitrogen equilibrium is notably less than during the febrile period. The following cases illustrate this fact.

	Range of maximum temperature.	Calories per kilogram.	N-intake.	N-balance.
Case 1:				
Febrile period	103.4–103.8	45	15	− 8.5
Convalescence	Normal.	41	13.5	− .3
Case 2:				
Febrile period	102.6–104.4	31	12.6	−11.3
Convalescence	Normal.	40	14.4	+ 1.8

Not only is less food required than during the febrile period, but Fr. Müller has shown that nitrogen may be retained by the typhoid convalescent on a diet which, with its low fuel value, is insufficient to maintain nitrogen equilibrium in health.

3. *Relapse.*—The number of cases which we have studied during relapses is relatively small, and the expression of a definite opinion concerning the food requirement would not be justified. Yet the evidence we possess indicates that the amount of food required to establish nitrogen equilibrium is large, though perhaps not so large as in the original febrile period. From a practical standpoint, the establishment of nitrogen equilibrium is relatively easy, because patients take their food more readily.

The following cases illustrate the food requirement during relapses:

	Range of maximum temperature.	Calories per kilogram.	N-intake.	N-balance.
Case 1	99.6-102.4	77	14.2	+3.7
Case 2	102.0-103.4	55	10.8	−3.8

THE PROTEIN, FAT, AND CARBOHYDRATE RATIOS.

I refer to this phase of the fever diet with some hesitation, because of the incomplete nature of the evidence. It has been our intention for several years to take up this problem specifically, but various circumstances have prevented. Yet there is evidence bearing upon the ratios which it seems worth while to present.

The protein ration.—The protein ration can not be considered without reference to the total energy value of the diet, consequently it will be assumed that the food furnishes sufficient energy.

The following observations concern the lower limits of the protein ration:

CASE 1.

Range of maximum temperature.	Calories per kilogram.	N-intake.	N-balance.
102.0-104.4	71	10.9	+0.9
102.4-104.8	70	2.4	−3.5

The diminution in the N-intake is the only essential difference which can be discovered in the two periods, and the opinion appears justified that the low N-intake in the second period is the cause of the change from the positive to the negative N-balance.

CASE 2.

	Calories per kilogram.	N-intake.	N-balance.
.4	54	7.7	−2.2
.2	45	14.0	+1.2

mperature range in the two periods is essen-
hough the energy value of the diet is somewhat
period, the increase of the N-intake from 7.7
apparently changes a negative to a plus balance.
h other evidence in our possession, suggest that
the optimum intake of nitrogen is approximately

cases relate to the higher limits of the optimum

CASE 1. RELAPSE.

Range of maximum temperature.	Calories per kilogram.	N-intake.	N-balance.
99.4–101.6	39	16.1	−7.8
101.8–102.2	40	22.7	−6.2

case, with but little difference in the temperature in the
ods, and no change in the energy value of the diet, an
of the nitrogen intake from 16.1 to 22.7 grams reduced the
n loss only 1.6 grams.

CASE 2.

Range of maximum temperature.	Calories per kilogram.	N-intake.	N-balance.
99.6–100.4	105	28.7	+15.7
100.2–100.6	70	28.2	+ 8.7

Here the reduction of the energy value of the diet from 105 to 70
lories per kilogram, though the intake of nitrogen remained at 28
rams, apparently caused the loss of 7 grams of nitrogen to the
ody.

The observations cited apparently justify the provisional assumption that the optimum nitrogen intake during the febrile period does not fall much below 10 grams or greatly exceed 15 grams a day. In convalescence the nitrogen intake has often exceeded 15 grams, with the general increase in the food, but we have not yet studied, experi-

mentally, the effects of so much nitrogen. Clinically, there has been no reason to think it objectionable.

The carbohydrate and fat rations.—We have seen that it is possible to establish nitrogen equilibrium in typhoid fever by the liberal use of carbohydrate. Conversely, the withdrawal of large amounts of carbohydrate from the diet is followed by the development of a minus nitrogen balance. The following case illustrates this:

Range of maximum temperature.	Calories per kilogram.			Nitrogen.	
	Total.	Fat.	CH.	Intake.	Balance.
102.8-103.6...	85	32	48	15	+0.6
103.4-103.8...	45	32	7	15	−8.5

While, at first sight, it might appear that the increased destruction of protein is the direct result of the withdrawal of so much carbohydrate, and while Dr. Shaffer and I were inclined to interpret it thus in an earlier paper, I personally have since been led to question the correctness of this interpretation. My present opinion is chiefly the result of clinical observation, though there is experimental evidence bearing upon the question.

In the experiment above summarized, not only have we to do with a diminution of the carbohydrate intake but with a decided reduction in the energy value of the diet. In this connection, it should be recalled that von Leyden and Klemperer succeeded in reducing the nitrogen losses in their cases by a large increase in the quantity of protein. Puritz had accomplished the same result. But I am disposed to believe that the saving of body protein was due to the energy which the additonal food protein supplied, rather than to its nitrogen.

Last year there was a case of typhoid fever complicated by glycosuria, in my service at Bellevue Hospital, in which it was necessary to reduce the carbohydrate ration to a minimum. In order to maintain the energy value of the diet, the fat was increased. The influence of the fat on the nitrogen balance is shown in the accompanying table:

Day.	Temperature.	Calories per kilogram.			N-intake.	N-balance.
		Total.	Fat.	CH.		
Twenty-first	99.2-103.6	50	32	10	17.1	−6.8
Twenty-second	100.0-103.0	35	24	5	11.4	−2.5
Twenty-third	98.0-101.0	54	36	10	17.9	−1.9
Twenty-fourth	98.4-100.8	76	50	16	20.5	+3.1
Twenty-fifth	98.8-101.8	78	51	17	23.8	+6.4

This case apparently shows that raising the energy value of the diet by means of fat, even though the carbohydrate intake is low, may change a minus to a plus nitrogen balance. Though the temperature was falling in the latter part of the period, convalescence was not established until the thirty-second day, and the results obtained in other cases (see Febrile period) make it improbable that the change in temperature was responsible for the alteration in the nitrogen balance. Likewise, it is scarcely probable that the saving of nearly 5 grams of body nitrogen was caused by the addition of 2.6 grams to the food. While the evidence of this case can not be considered as conclusive, it is very suggestive. Moreover, I have repeatedly observed, clinically, when a patient's tolerance for carbohydrate (meaning by this his ability to take it without its causing alimentary disturbances) has been reached, without the food furnishing what appeared to be sufficient energy, that his condition has been perceptibly improved by increasing the amount of fat. In fact, fat furnishes from one-third to one-half of the total energy of the diet which we ordinarily employ.

Benedict and Surányi thought that a high carbohydrate diet caused a greater retention of nitrogen in typhoid fever than a high fat diet, and Grafe has emphasized the importance of carbohydrate in the fever diet.

Without any intention of minimizing the importance of carbohydrate, I believe that the fat ration should be large. I shall not venture, however, to express an opinion concerning the optimum proportions of fat and carbohydrate in the fever diet.

Absorption.—In consideration of the very large amount of food which we employ it became necessary to investigate the ability of the typhoid patient to absorb it.

Our diet has been criticized adversely on the ground that the quantity of food was greater than could be absorbed by the ulcerated intestine. Von Hoesslin's work upon the absorption of moderate amounts of food in typhoid fever had been confirmed by Puritz. There was no clinical evidence that the food was not absorbed by our patients. The stools possessed an unusually normal (for typhoid fever) appearance. Diarrhea was seldom observed, and usually disappeared under the influence of the diet when patients entered the hospital suffering from it. Yet evidence of the proportions of the different foodstuffs actually absorbed was desirable, and at my suggestion Dr. Eugene F. Du Bois analyzed the feces of a series of cases, taking from 2,500 to 4,500 calories a day.[3]

When carbohydrate was given in amounts up to 450 grams a day, the loss in the stools was less than one-half of 1 per cent. Protein was given in quantities which averaged more than 100 grams a day,

yet the feces nitrogen never reached 2 grams. It averaged 1.12 grams, which is a normal figure for such a diet. The average loss of fat in the period of high fever, when the food contained 150 to 200 grams a day, was 7.2 per cent. Later in the disease, patients took from 200 to 327 grams of fat a day, with a loss of 4.5 per cent, which is only slightly higher than normal.

Indican, which is present in large amounts early in the disease, becomes less and less as the temperature falls until, in convalescence, it appears only in traces.

These results prove that the large amount of food required by the typhoid fever patient is readily absorbed.

THE RESPIRATORY EXCHANGES IN TYPHOID FEVER.

With the assistance of Dr. Eugene F. Du Bois,[4] I undertook last fall to study the respiratory exchanges in typhoid fever with the aid of the Benedict "unit apparatus."[5]

The scope of the work was general; that is, it was limited for the most part to a determination of the influence of the high calory diet upon metabolism in typhoid fever.

The majority of the studies which have previously been made have been upon patients in the fasting state. Nearly all of our readings were taken within a relatively short time after food.

The diets given contained 10 to 20 or more grams of nitrogen, 100 to 300 or more grams of fat, and up to 900 grams of carbohydrate a day. They had energy values of 2,500 to 7,500 calories.

No patient was studied who was temperamentally unfitted for the use of the apparatus; that is, who became nervous while on the machine after the first one or two readings. No patient was studied whose breathing was irregular or labored.

Efficiency tests were made once a week or oftener.

The majority of readings were taken by three observers.

Dr. Benedict himself was kind enough to oversee our technique during an afternoon's work.

The respiratory quotient.—We made in all about 150 determinations of the quotient. Some 30 of them have been excluded from our protocols, because of obvious or suspected errors of technique. If any of the three observers raised a question of accuracy respecting the behavior of the patient or of the apparatus, the reading was rejected.

The usual period of observation was 15 minutes, during which time the patient lay at complete rest, oftentimes falling asleep.

The time allotted me will not permit a discussion of the relative merits of short and long periods of observation.

Our study covers part of the febrile period, the earlier period of convalescence, and relapses.

Fifty-six quotients were taken in the febrile period, 41 in convalescence, and 10 in relapses. The largest number of quotients were

taken in the third and fourth weeks of the febrile period, and in the first and second weeks of convalescence.

Febrile period.—Third week: The lowest quotient taken in this stage of the disease was 0.70, the highest was 0.96. The majority of the quotients were above 0.85.

Fourth week: The lowest quotient obtained in this stage of the disease was 0.73, the highest was 1.002. The majority of the quotients were just below or above 0.90.

It is evident that the quotients ranged higher in the fourth than in the third week of the disease. The change in the level of the quotient was so constant and so striking that we have interpreted it as indicating a definite change in metabolism in the last days of the fever. If this interpretation is correct, convalescence manifests itself in the process of metabolism before the temperature reaches normal. Since this change in metabolism has not been observed by other investigators, in the case of patients who have been partially starved, it probably is a result of the liberal feeding. There is clinical evidence that convalescence is materially shortened by the liberal diet.

Convalescence.—There is a decided rise in the quotient in the first week of convalescence; the lowest quotient was 0.82, the highest was 1.16, the majority of the quotients being above 0.95.

The rise of the quotient is maintained in the second week of convalescence.

In the third week of convalescence, the quotient, in the few observations which we have made at this stage exhibits a tendency to fall toward the normal.

These results are in striking contrast to those of Svenson, in particular, where a definite rise in the quotient was delayed until the second and even the third week of convalescence. In Svenson's cases the quotient did not begin to fall until in the fourth week or later.

Relapse.—The few quotients which we have taken during a relapse manifest a tendency to range somewhat higher than quotients in the original fever. The lowest quotient was 0.80, the highest 1.043.

Attention should be directed to the fact that quotients of 1 or over were obtained in the last days of the febrile period, frequently in the first two weeks of convalescence and with less frequency during relapses. The gains in weight and the general improvement in the patients' condition which commonly occurred in convalescence had led to the assumption that the formation of fat was in active progress; but it was with surprise that the transformation of dextrose into fat was observed to occur in a relapse while the temperature was 102.2° F.

O_2 *consumption.*—The O_2 consumption varied in general between 4 and 6 cubic centimeters per kilogram and minute, averaging about

5 cubic centimeters. It did not in any case fall below or exceed these limits in the second or third weeks of the febrile period.

In the fourth week it fell to 3.8 and 3.9 in two readings and was above 6 cubic centimeters in 8 readings (the highest being 6.6 cubic centimeters).

In the patients studied by Kraus, Grafe, and Rolly the O_2 consumption averaged about 5 cubic centimeters in the febrile period, never falling below 4 cubic centimeters, and in only a few instances rising above 6 cubic centimeters (the maximum being 6.5 cubic centimeters).

The normal consumption of O_2, according to Magnus-Levy, varies between 2.8 and 4.5 cubic centimeters per kilogram and minute. The O_2 consumption in Cetti, before the first meal after his fast, was 4.67; after the first meal it was 5.05 cubic centimeters (Zuntz and Lehmann).

From these considerations it is evident that the liberal diet does not greatly increase the O_2 consumption in the febrile period.

During the first week of convalescence the majority of our patients used 5 cubic centimeters or more of O_2 per kilogram and minute. The lowest reading was 3.5 cubic centimeters; the highest was 6.5.

During this week there was a definite tendency for the respiratory quotient to rise, which was due to an increase in the amount of CO_2 eliminated rather than to a diminution in the O_2 consumed.

This likewise is in striking contrast to the results of Svenson, Grafe, and Rolly, where a decided diminution in the O_2 consumption occurred with but little if any change in the level of the respiratory quotient as compared with that of the febrile period. The diminution in the O_2 consumption observed by these authors has been interpreted to indicate either an attempt of the body to economize its resources or exhaustion of the cells (Svenson).

Heat production.—The study of the heat production by man in fever has been limited so far to the method of indirect calorimetry. While the method is not free from objections, the margin of error is not believed to exceed 5 to 10 per cent.

The febrile increase in heat production was observed in all of our patients. Since we have had no opportunity to study the heat production in any of them after their return to health, I shall not attempt to calculate the percentage increase caused by the fever in the different cases.

The heat production in our patients averaged about 35 to 38 calories per kilogram per day.

In the febrile period the greatest amount of heat produced was 45.9 calories per kilogram (in a relapse 48.7 calories per kilogram [a]), the smallest was 28 calories per kilogram.

The greatest amount of heat produced during convalescence was 42.4 calories per kilogram; the smallest was 26.1 calories per kilogram.

The heat production was not greatly increased by food. For example—

FIRST CASE.

Fourteenth day; temperature at time of observation, 103.2° F.; received in his food, 35 calories per kilogram; produced, 35.8 calories.

Twenty-fourth day; temperature at time of observation, 100.2° F.; received in his food, 76 calories per kilogram; produced, 34.2 calories.

Thirty-fifth day; First period, temperature at time of observation, 98.4° F. received in his food, 83 calories per kilogram; produced, 42.9 calories. Second period (temperature at time of observation 99.6° F.); received in his food, 83 calories per kilogram; produced, 36.1 (1 hour 44 minutes later).

SECOND CASE.

Thirty-first day; temperature at time of observation, 102.2° F.; received in his food, 38 calories per kilogram; produced, 36.7 calories.

Thirty-ninth day; First period, temperature at time of observation, 100.2° F. received in his food, 90 calories per kilogram; produced, 32 calories. Second period, temperature at time of observation 100.2° F., received in his food, 90 calories per kilogram; produced, 28.9 calories.

The bearing of these results upon the specific dynamic action of foods in fever must be left for future consideration. However, the conclusion is warranted that the high calory diet is not contraindicated on the ground that it increases the heat production too greatly.

In considering the heat production, this important question comes up: If a patient produces only 35 calories per kilogram, for example, what benefit can accrue from the administration of such large amounts as 60 to 90 to even 170 calories per kilogram? Why is not the amount of food which will just cover the heat production sufficient for the patient?

The studies of von Leyden and Klemperer, as well as those of Shaffer and Coleman, clearly show that an amount of food just, or but little more than, sufficient to cover the heat production (estimated upon later observations) will not protect the body protein or keep the patient in weight equilibrium. In order to accomplish this, from 60 to 90 and more calories per kilogram a day are required.

The first question which arises is, has such an amount of food actually been given? In the study of the protein metabolism, by Shaffer and Coleman, all of the food was weighed or measured and the amount taken was accurately known.

While in our work last year circumstances rendered it impossible to weigh all of the food, we have perfect confidence in the accuracy of the estimations. The food was administered by Miss Mary E. Sheehan, who has been associated with the work for the past three years, or under her immediate supervision. The errors which might

have occurred affected chiefly such articles of food as cereal, potato, and apple sauce, which constituted relatively only a small part of the intake. The quantities of milk, cream, bread, butter, lactose, and eggs could be controlled with reasonable certainty.

While I can speak only of typhoid fever, I can assert positively that in this disease nitrogen and weight equilibrium can not be maintained without an excess of food amounting ordinarily to 100 to 200 per cent over the heat actually produced (as measured by indirect calorimetry). Since the maintenance of nitrogen and weight equilibrium in fever signifies, by all known standards, the optimum state of nutrition, it may be accepted that the excess of food is required.

But what becomes of the excess? What purpose does it serve?

We are at present engaged in the study of this problem. The determination of the water balance, and more carefully controlled observations upon variations in weight than we have been able to make, will undoubtedly aid in its solution.

The method of indirect calorimetry is admittedly faulty, but the error probably does not exceed 5 per cent. An allowance of 10 to 15 per cent should be made for the movements of the patient about the bed, since he is at absolute rest only during the period of observation. Allowing also an error of 10 per cent in the estimation of the food intake, the maximal allowance for error and muscular work amounts to only 30 per cent. Deducting this from the total increase of food, from 70 to 170 per cent of the excess over the heat production remains to be accounted for.

In convalescence patients often gain from one-half to 1 pound a day, and, as has been pointed out, the formation of fat from dextrose is in active progress. Therefore, it is possible to account for at least a large portion of the excess of food in this stage of the disease. It is in the febrile period that the difficulty of accounting for it arises. Patients occasionally gain weight in this period, but slight loss occurs in the majority. Though the formation of fat from dextrose has been observed in the last days of the fever, and once in a relapse when the temperature was 102.2° F., such transformation has not been observed in the more active phases of the febrile period. Fat, as well as carhohydrate, is consumed when the fever is at its height.

The excess of food is not passed out in the feces as unabsorbed residue, as the absorption experiments show. Glycosuria has been discovered only once. The greatest amount of sugar which this patient lost in any one day was 79 grams, corresponding to 5.8 calories per kilogram. While we have not yet determined the C:N ratio of the urine, it does not seem probable that an oxidizable

substance (other than sugar) in sufficient quantity to explain the discrepancy should hitherto have escaped detection.

The calculated heat production makes it certain that the excess of food is not, immediately at least, converted into energy.

The change in the level of the respiratory quotient in the last days of the fever, and especially in the first week of convalescence, is due to an increase in the CO_2 output, which indicates that more carbohydrate is metabolized. Since this occurs ordinarily without any increase in the amount of food taken, the question naturally arises whether more carbohydrate becomes available as the toxins cease to be formed, because they cease to be formed.

THE PROPORTIONS OF PROTEIN, FAT, AND CARBOHYDRATE METABOLIZED DURING THE PERIODS OF OBSERVATION.

We have made as yet only a limited number of observations upon the proportions of protein, fat, and carbohydrate metabolized in fever, but the results which we have obtained agree in general with those of Grafe and Rolly.

Protein.—The percentage of energy derived from protein is greatest during the febrile period, and diminishes as convalescence approaches. In one of our patients the percentage of energy thus derived ranged from 19.2 to 29.2 per cent, from the fourteenth to the twenty-eighth days of the febrile period; from the thirty-second to the thirty-ninth days (early in convalescence) the percentage gradually dropped from 19 to 10 per cent.

According to Grafe, the percentage of energy derived from protein varies also with the height of the temperature. With temperatures under 39° C. he found the mean to be 18 per cent, with temperatures over 39° C. the mean was 20.6 per cent. Senator believed that Grafe had calculated the proportion of protein metabolized too low. While our observations will not permit us to express a definite opinion, we are disposed to agree with Senator in this particular.

Fat.—The percentage of energy derived from fat apparently depends directly upon the amount of available carbohydrate. Indirectly it depends upon the height of the temperature and the stage of the disease. These statements are illustrated by the following observations:

CASE 1.—RELAPSE.

	Temperature at time of reading.	Calories per kilogram produced.	Time after food.	Respiratory quotient.	Per cent from fat.
			° ′		
First period	100.2	43.9	3 7	0.862	35.1
Second period	100.2	40.9	31	.922	13.3
Third period	100.2	43.1	1 17	1.006	0.0

CASE 2.

Day of disease.	Temperature at time of reading.	Calories per kilogram produced.	Time after food.	Respiratory quotient.	Per cent from fat.
Fourteenth day	103.2	35.8		.858	28.4
Twenty-fourth day	100.2	34.2		.771	[1] 60.6
Thirty-second day:[2]					
First period	98.8	36.7		.927	11.1
Second period	98.8	38.2		.993	0.0

[1] Forty-six minutes after 10 grams carbohydrate. Patient had received 28 grams carbohydrate 3 hours previously.
[2] First day of convalescence.

Carbohydrate.—Carbohydrate furnishes the greatest percentage of energy whenever it is available in sufficient quantity, as is illustrated by the following observation:

RELAPSE.

	Temperature.	CH.	Time after.	Respiratory quotient.	Per cent from CH.
			° ′		
First period	102.2	108	1 23	1.043	86.5
Second period	102.2	143	1 57	.973	85.9
Next day:					
First period	100.2	71	3 7	.862	48
Second period	100.2	65	31	.922	69
Third period	100.2		1 17	1.006	83

Carbohydrate is oxidized most rapidly in the febrile period and the supply is soon exhausted, as the following observations show:

CASE 1. FEBRILE PERIOD.

	Temperature.	CH.	Time after.	Respiratory quotient.	Per cent from CH.
			° ′		
Fourteenth day	103.2	70	2 27	.856	45.5
Sixteenth day	103.0	70	3 57	.770	16.2

CASE 2. CONVALESCENCE.

Tenth day:			° ′		
First period	98.0	123	2 28	.986	[1]
Second period	98.0		3 43	1.035	
Third period	98.0		4 56	.976	

[1] Urinary nitrogen not determined.

These results justify the clinical procedure of frequently administering large quantities of carbohydrate to the fever patient.

The rapidity with which the carbohydrate is utilized suggests that it is burned without being transformed into glycogen by the liver.

Clinical.—In conclusion, I may be permitted to speak briefly of the clinical effects of a liberal diet in typhoid fever. After all is said, the value of any diet must be judged by the results obtained from its use.

The influence which a diet exercises upon the course of typhoid fever—that is, its duration, mortality rate, incidence of complications, and frequency of relapses—can be learned only from the study of a large number of cases extending through epidemics of varying virulence, but the effects of a diet upon the patient may be learned from the study of a few cases by the inductive method of reasoning.

There are only two possible sources of energy either in health or in disease, namely, food and the tissues of the body. If the food is insufficient, the tissues of the body are drawn upon to furnish the energy which is necessary for the continuance of life. Since it has been proved to be possible to prevent tissue loss in typhoid, the essential question regarding the fever diet is, Shall the fever patient be deliberately starved? The burden of proof rests upon the advocates of starvation.

As was stated earlier in the paper, the methods of complete and partial starvation have been tested in fevers during a period of 2,000 years. Many practitioners still starve their fever patients, but apparently it is because they fear that sufficient food may injure the intestine, or cause disorders of digestion, rather than that they consider starvation in itself beneficial. Few will deny that the starvation treatment of fevers has been a failure.

The practice of supplying fever patients with all the food they require, or at least all they can digest and absorb, has been in use for only six years. Yet the benefits of the procedure are already evident. Not only is the course of the disease favorably influenced, but the condition of the patient is vastly improved. The duration of the febrile period appears to be unaffected. The mortality rate is lowered. The severity of the infection is lessened. It is too early to speak with certainty of the incidence of complications or the frequency of relapses, but complications and relapses appear to be better borne by the patient. Other striking results of the liberal diet are the absence, or disappearance, of severe toxic symptoms; the alert mental condition; the absence or disappearance of diarrhea, which, as Kendall has shown, is due to the liberal supply of carbohydrate; the maintenance of weight; the rapidity with which convalescence proceeds; and the prevention of the prolonged disability which formerly so often followed an attack of typhoid fever.

[1] As has been shown by DuBois, the allowance of 15 per cent loss of food nitrogen in the feces was excessive. Recalculated on the lower basis, the results make a better showing.

[3] All of the cases used to illustrate the total food administered and the protein, fat, and carbohydrate ratios, with one exception, have been taken from the paper by Shaffer and Coleman, already mentioned.

[4] Archives of Internal Medicine. 1912, x, 177.

[5] I regret very much that the custom of the congress forbids joint authorship of the communications presented before it, otherwise his name would be associated with mine. We shall publish the details of the investigation together.

[6] Our instrument was not then equipped with a spirometer.

[7] This patient was a boy of 17 years, who received 170 calories per kilogram the day of the observation.

DISCUSSION.

Dr. PLÖNIES, Hannover: Ich vermisste bei der Besprechung der Diät für die verschiedenen Krankheiten den Hinweis auf das Verhalten der Herzgrösse und das Ergebniss der Stuhluntersuchung für die Auswahl der Diät, ohne die ich eine Diät nicht aufstellen würde im einzelnen Krankheitsfalle. Natürlich muss auch beachtet werden, ob die Schleimhäute des Magenkanals intakt sind. Auf das Nähere kann ich hier nicht eingehen.

Dr. VON NOORDEN: There is now a tendency to prefer and to recommend foodstuffs of high caloric value, or, in other words, foodstuffs in which the single calorie is as cheap as possible.

This is a point of view which is allowed to the political economist, but should not be the principal point of view of the hygienist.

In viewing the subject from such a standpoint, we should disapprove a great many foodstuffs which are of greatest value for the digestion and the maintenance of good health. So we heard today the cortical parts of the wheat and rye seeds disapproved by Prof. Rubner, and the same we heard with regard to raw fruit. Indeed, it causes a higher price of the bread calorie and the fruit calorie, if you add the pericarp to the flour, and, of course, by doing so, you increase the bulk of feces. But you will thereby improve the whole process of digestion, and you will fortify the functions of the intestines. I consider it as a kind of education for the intestine if you give a rather coarse food; and, on the other hand, you would spoil the intestine, and you would increase its tendency to disease, if you omitted the "roughage" of the foodstuffs. I mean this fact must be more considered than is nowadays the habit.

Prof. LONG: With reference to the remarks of Prof. Rubner, it should be said that properly canned meat, so cooked as to leave most of the extract in the meat, as put up by some of our firms, is entirely satisfactory. Much of our canned meat, however, is prepared from a relatively low grade of cattle, and the meat is frequently overcooked, and then imperfectly salted. Such meat is not, in the long run, very satisfactory.

In regard to pasteurized milk, the experience in this country is to the effect that in the "holding" process, when properly carried

out, the temperature not being allowed to go above 60° C., the quality of the milk is not practically injured, and, in all reasonable requirements, is the full equivalent of the fresh milk, besides being practically safe for use.

Dr. LANGWORTHY: One problem, in feeding quantities of fat, is to give a dish which resembles one the subject likes. Cornstarch pudding, highly flavored with caramel, has proved very useful for this purpose in the work of the United States Department of Agriculture. As made with a high fat content, it can be eaten without distaste for three-day experimental periods.

Prof. LUSK: There is need that scientific knowledge of the fuel value of foods be more popularly extended. It should be known that bread, butter, and milk are of food value, and that flavors, like tea and meat extracts, have no available energy. The poor of the cities should be taught such things, perhaps best through their own locally influential boards of health. It would be highly desirable, furthermore, to found a national society of educated people, who could be united in a common endeavor to introduce into the national life and law of the people the benefits of scientific knowledge, now too often confined in the hands of the few. The close connection between science and government in Germany affords an example to be copied.

Prof. HOLST: I wish to point out again, that a boiling of nutriments at temperatures exceding 100° C. is an error. If you feed a chicken on meat boiled at 100° C. only, it does not become ill. If, however, the meat is boiled for half an hour at 110° C. or 120° C., it produces polyneuritis. The same applies to scurvy and cabbage. If you boil cabbage at 100° C., it prevents the experimental scurvy. But if you boil it for half an hour at 110° C., it loses a good deal, and if you boil it for half an hour at 120° C., it loses most of its antiscorbutic properties. Therefore, when a boiling at 110° C. for one-half hour is used in the kitchens of our hospitals, this must be characterized as a wrong method.

TUBERKULOSE UND STOFFWECHSEL.

Dr. DIESING, Chief Physician, Recreation and Convalescent Home, Gross-Hansdorf, Hamburg, Germany.

Wie alle Infectionskrankheiten ruft auch die Tuberkulose eine Reihe von allgemeinen Erscheinungen hervor, die wir als Abweichungen vom normalen Stoffwechsel betrachten müssen. Fieber, Abmagerung, Schwäche, Schweisse, Anämie, Störungen der Menstruation, Neurasthenie, u. s. w., sind charakteristisch für den Ablauf einer chronischen Tuberkulose-Erkrankung. Alle diese Störungen sind Erscheinungen eines beschleunigten Stoffwechsels, einer energischeren Oxydation, einer schnelleren Verbrennung der Körpersubs-

tanz, einer Demineralisation des Organismus. Dass der Tuberkelbacillus der Urheber dieser Beschleunigung der oxydativen Vorgänge ist, unterliegt keinem Zweifel, der Tuberkelbacillus flicht seinen eigenen Stoffwechsel in den Stoffwechselablauf seines Wirtes ein und lenkt diesen damit in falsche Bahnen. Die Endprodukte des Bacillenstoffwechsels, seine Toxine sind uns bekannt, auch kennen wir die vom Wirtsorganismus producierten Gegengifte, die Antitoxine. Eine fast unübersehbare Fülle von höchst verdienstlichen Arbeiten liegen auf diesem Gebiete vor. Aber die Forschung hat sich bis heute mit dem Anfangsgliede der Kette noch nicht abgegeben, sie hat sich nicht darum bekümmert, welche Stoffe des Wirtsorganismus der Tuberkelbacillus angreift und aus ihrer physiologischen Bindung freimacht, wie er sie verändert, auf dass sie eine so unheilvolle Thätigkeit ausüben können. Da die Toxine und Antitoxine im Blutserum entstehen, so kann man ohne weiteres annehmen, dass das Blut die Stelle ist, wo der Tuberkelbacillus unheilvoll in den Stoffwechselablauf seines Wirtes eingreift. Die nächste Frage, die man danach logischerweise stellen muss, aus welchen Elementen des Blutes entnimmt der Tuberkelbacillus seine Nahrung, glaube ich aber beantworten zu können, wenn ich wiederum darauf hinweise, dass eine zu energische Oxydation, ein zu reichlicher Zutritt von Sauerstoff zu den Geweben des tuberkulösen Organismus gerade das Moment, ist, dass den Stoffwechsel des Tuberkulösen von dem des Gesunden unterscheidet. Der Träger des Sauerstoffes im Blute ist aber das Haemoglobin und in diesem speciell das eisenhaltige Haematin. Das eine im Haematin enthaltene Atom Eisen wirkt als Katalysator und beschleunigt die Oxydationen im Organismus. Wenn nun im tuberkulösen Organismus der Ablauf der oxydativen Vorgänge so beschleunigt ist, so kann das nur darin seine Ursache haben, dass der Tuberkelbacillus grössere Mengen dieses Katalysators freigemacht, also entsprechende Mengen Haematin von dem begleitenden Eiweisskörper, dem schwefelhaltigen Globin, abgetrennt hat. An dieser Stelle muss meines Erachtens eine rationelle Therapie der Tuberkulose einsetzen. Nicht mit den Stoffwechselendprodukten des Bacillus den Körper des Kranken noch weiter vergiften, sondern das Haemoglobin für den Tuberkelbacillus unangreifbar machen, muss das Ziel unserer Therapie sein.

Die bisher überwiegend geübte physikalische Therapie der Tuberkulose: die Zufuhr reiner frischer Luft, die Darreichung einer kräftigen, reizlosen Kost, die Liegekur, der Aufenthalt im Mittel- oder Hochgebirge, neuerdings auch die Vermeidung aller alkoholischen Getränke, setzt sich vorzüglich aus Massnahmen zusammen, die geeignet sind, den Sauerstoffverbrauch herabzusetzen und die Verbrennung von Körpersubstanz möglichst hintanzuhalten. Insofern

hat die Empirie bis jetzt einen ganz richtigen Weg eingeschlagen. Für die Wirkung des Höhenklimas bedarf das noch einer weiteren Erklärung. Unsere Atmosphäre ist so zusammengesetzt, dass mit zunehmender Höhe die Menge des Sauerstoffs ab- und die Menge des Stickstoffs zunimmt, der Partiardruck des Sauerstoffs ist in den höheren Schichten unserer Atmosphäre herabgesetzt, es wird also den Lungen in der Atmungsluft weniger Sauerstoff zur Verfügung gestellt, was notwendigerweise eine Eineschränkung der oxydativen Vorgänge im Organismus zur Folge haben muss.

Wie können wir nun noch weiterhin den Stoffwechsel des Tuberkulösen beeinflussen, auf dass er seine Oxydationen einzuschränken gezwungen wird? Zur Beantwortung dieser Frage hat mich folgende Erwägung geleitet: die empirische Formel des Haemoglobin zeigt neben den hohen, nicht ganz gleichmässig angegebenen Atomzahlen des Kohlenstoffs, Sauerstoffs, Stickstoffs, und Wasserstoffs 1 Atom Eisen und 3 Atome Schwefel. Diese 4 Mineralatome sind nach meiner Anschauung die starken chemischen Anker, die das so hoch zusammengesetzte Molekel des Haemoglobins zusammenhalten. Wollen wir nun das Eisenatom noch fester an das Haemoglobin binden, als es physiologisch schon der Fall ist, um es vor den Angriffen des Tuberkelbacillus zu schützen, so müssen wir die 3 Schwefelatome zu verstärken suchen. Dieses Ziel können wir durch eine passende Schwefelzufuhr zum Organismus erreichen.

In jahrelangen Versuchen habe ich so ziemlich all in Betracht kommenden Schwefelpräparate in äusserer und innerer Anwendung bei Tuberkolose versucht und bin schliesslich durch eingehende mikrochemische und massanalytische Untersuchungen zu einer dem thierischen Organismus eigentümlichen Schwefelverbindung, dem schwefelhaltigen lipoiden Farbstoff der Nebenniere, gelangt. Mit diesem von mir Adrenochrom genannten Organextrakt habe ich bisher über 300 Fälle von Tuberkulose aller Grade und aller Formen behandelt, und habe in einem grossen Parallelversuch mit Tuberkulin bedeutend bessere Resultate als mit dem letzteren Mittel erlangt. Die Anwendung des Adrenochroms ist übrigens durchaus ungefährlich, und führt bei richtiger Dosierung keinerlei unangenehme Nebenwirkungen mit sich. Es würde mich zu weit führen, wenn ich hier eine Statistik oder eine Kasuistik meiner Fälle geben wollte, auch möchte ich hier von vornherein erklären, dass man mit diesem Verfahren keine verzweifelten Fälle im Endstadium heilen kann, aber immerhin ist es mir doch in allen Fällen gelungen, eine beträchtliche Verlängerung des Lebens und eine unverkennbare Milderung aller Beschwerden der letzten Lebensperiode solcher unglücklichen Menschen zu erreichen. Leichte und mittelschwere Fälle werden mit meinem Verfahren schneller geheilt als es bei Anwendung der physikalischen Heilmittel allein möglich ist.

THURSDAY AFTERNOON, SEPTEMBER 26, 1912.

THE UNKNOWN FACTORS IN THE ILL EFFECTS OF BAD VENTILATION.

YANDELL HENDERSON, Ph. D., Professor of Physiology, Yale Medical School, New Haven, Conn.

It is one of the cardinal principles of modern hygiene that bad ventilation of dwellings, factories, shops, and cars is detrimental to health. Fresh air has in fact become almost a fetich. The open-air treatment of tuberculosis is assuming each year a more important part in medicine. The marked improvement in cases of pneumonia obtained by putting them in the open air is testified to almost universally by those who have tried it. In view of these facts, the statement which I am about to make sounds almost unbelievable. The statement is this: We have really, at the present time, no adequate scientific explanation for the health-stimulating properties of fresh air and the health-destroying influences of bad ventilation.

In such a statement it is necessary to limit the meaning to the effects of the air itself and not to include the effects of dust, the effects of deprivation of sunlight, the effects of sedentary habits, long hours of work, and other unsanitary conditions. Even when all of these elements are left out, however, it is clear that close-crowded, ill-ventilated rooms act upon the majority of persons and produce immediate ill effects. Those who are particularly sensitive are liable to headaches, nausea, giddiness, and even vomiting or fainting. To what are these effects due? It is my purpose to-day to consider briefly our knowledge, or rather our ignorance, of the subject, and to make a suggestion along a somewhat new line.

In this problem scientific progress has in the main served only to eliminate possible explanations. When Lavoisier discovered that breathing consists in the absorption of oxygen for the vital combustion, and the elimination of the carbonic acid which the combustion produces, the problem seemed to have been solved. The manifest answer was "lack of oxygen." Even at the present time it is quite common to hear the expression that "the air of a close and crowded room has been deprived of its oxygen." The analogies of the kerosene lamp smoking because of an insufficiency of air supply or of a fire in a stove extinguished by closed dampers have become firmly fixed in the popular mind. Every school child is taught that a mouse sealed up in a small glass jar dies in a short time. It is unnecessary to review scientific investigation at any length, however, to prove that none of these facts have really any bearing on the

problem before us. It is well established that even in the closest hall packed with people the oxygen content of the air is practically never reduced by as much as 1 per cent. On the other hand, it is only necessary to go a short distance up into the mountains to come under an atmospheric pressure such as to reduce the oxygen supply much more than this amount, and yet mountain air is especially healthful. Moreover, the administration of pure oxygen to cases of tuberculosis has proved of no value, and it is extremely doubtful whether the use of oxygen in pneumonia is of any value. From such facts, and they could be almost indefinitely multiplied, it is clear that the amount of oxygen in the air has little or nothing to do with its stimulating or depressing properties in ordinary life or in disease.

Hygienists are accustomed to estimate the effectiveness of ventilation by the amount of carbon dioxid which the air in a room contains. It is quite certain, however, that a quantity of carbon dioxid tenfold greater than the highest hygienic limit may be breathed practically indefinitely with impunity. To mention only a single fact indicating this, take such respiration experiments as those carried out in a closed calorimeter in the Carnegie laboratory in Boston. The subject in such an apparatus breathes an atmosphere which frequently contains considerably more than 1 per cent of carbon dioxid. In this he remains for days, or even weeks, and performs active mental or physical work with no ill effects whatever, yet the standard which hygienists are accustomed to use in estimating the purity of air limits the carbon dioxid to amounts so small as "parts in ten-thousandth," with 0.13 of 1 per cent as an upper limit. For more than 50 years it has been recognized that carbon dioxid, in itself, has little or nothing to do with the relations of air to health. Pettenkofer's standard for estimating ventilation by the carbon-dioxid content of the air has continued to be used merely as a convenient index.

In the experiments of Brown-Sequard and d'Arsonval, published in 1887, the idea was advanced that the toxic effects of expired air are due to a volatile poison contained in the breath. Their experiments have been so frequently quoted that it is quite unnecessary for me to review them here. As the result of a long series of investigations by many workers, it seems to have been shown beyond all question that the breath contains no such "anthropotoxin." This was the conclusion reached, for instance, by Mitchell, Billings, and Bergey, while Formanek concluded from an extended review of the subject that the only substances appearing in the breath, other than carbon dioxid and water vapor, are the products of putrefaction in the mouth, particularly ammonia.

This chapter seemed to have been closed when, about a year ago, Rosenau and Amoss[1] revived the conception of the toxicity of the

breath in a new form. They condensed the vapor of the air expired by human beings and injected the liquid into guinea pigs. A second injection, the proper number of days later, showed that the pigs had become sensitized to some substance contained in the injected liquid. It is only fair to Rosenau and Amoss to say that, in stating their experiments, they have not claimed for them that they afford necessarily a complete explanation of the problem before us, but the suggestion that they may offer such an explanation is clear. Their more recent work along this line is, I understand, to be offered before this section of this congress. Unless, however, it goes much further than their earlier work, I must express my incredulity regarding its significance for the problem before us. There is nothing, so far as I am aware, in our present knowledge of anaphylaxis, to suggest that any species of animal can be sensitized to a protein produced by itself. It may well be that a small amount of albuminous material is carried by the expired air. If so, we should expect that guinea pigs might thereby become sensitized to human protein; but it is quite another thing to suppose that human beings can be sensitized to human protein. Another objection which weighs strongly, it seems to me, against this suggestion, is that the clinical picture presented by a person in a close and crowded room is altogether different from that of anaphylactic shock. If the suggestion of Rosenau and Amoss were correct, we should expect that persons in a close and crowded room would develop a coryza, conjunctivitis, and asthma. I say that we might expect this, for the reason that this is what happens in those unfortunate persons who are afflicted with hay fever, and particularly in those who, while indifferent to all other forms of dust and pollen, are susceptible to the skin and breath emanations of horses. In fact, in that form of hay fever which consists in sensitiveness to the exhalations of horses, we have exactly the sort of thing which, as Rosenau and Amoss suggest, is responsible for the ill effects of bad ventilation. It is evidence of some value against their suggestion, therefore, that the symptoms induced by the two sets of conditions are totally different.

A good many years ago Hermann suggested that in reality the ill effects of bad ventilation are due not to the chemical composition of the inspired air but to interference with the heat eliminating function of the skin. This view has been elaborated and placed upon a very firm experimental basis in recent years by Flügge[2] and his pupils. All of their experiments were carried out upon man. The subject was inclosed in an air-tight box of small size and the experiments were planned so as to contrast the effects of chemical vitiation of the atmosphere, on the one hand, with the physical changes of high temperature and humidity, on the other. It was found that a high degree of chemical vitiation (i. e., reduction of the oxygen and in-

crease of the carbon dioxid) was borne with no perceptible ill effects, so long as the air in the chamber was kept cool and dry. On the other hand, all of the ill effects of vitiated air were experienced, with even a slight chemical impurity, as soon as the temperature and moisture content rose sufficiently to interfere with the elimination of heat through the subject's skin. Particularly striking was one experiment in which one subject, placed within the chamber in a hot, moist, and chemically highly vitiated atmosphere, experienced all the ill effects of bad ventilation, although at the same time he was allowed to breathe fresh and perfectly pure air from outside, through a mouthpiece in the wall of the chamber. At the same time another subject outside of the chamber breathed through a mouthpiece connected with the interior. The skin of the latter was of course under hygienic conditions. His air supply was supposedly highly unhygienic, but no ill effects were experienced. On the other hand, the subject within the box whose lungs received fresh air, but whose skin was exposed to a hot and moist atmosphere, felt dizzy and became nauseated.

Very similar results have been reported by Leonard Hill [3] in England. Hill described one of his experiments in which he and several of his pupils were shut up in a small chamber, as follows:

> After 44 minutes the dry-bulb thermometer stood at 87° F., the wet bulb at 83° F. The carbon dioxid had risen to 5.26 per cent. The oxygen had fallen to 15.1 per cent. The discomfort felt was great; all were wet with sweat and the skin of all was flushed. The talking and laughing of the occupants had gradually become less and then ceased. On putting on the electric fans and whirling the air in the chamber the relief was immediate and very great, and this in spite of the temperature of the chamber continuing to rise. On putting off the fans the discomfort returned. The occupants cried out for the fans. No headache or aftereffects have followed this type of experiment, which has been repeated five times..

In the light of these facts we seem to be forced to the conclusion that the effects of bad ventilation are not dependent upon the air which enters the lungs, but upon the temperature, moisture content, and drafts of the air in contact with the surface of the body. They depend upon interference with heat elimination by the skin. They are due wholly, or almost wholly, to heat stagnation in the atmosphere contained in the pores of the clothing surrounding the body.

What I wish to put before you now is a question. Is this explanation satisfactory? I must confess that for me it is not. From the standpoint of hygiene, it is indeed practically proved. From the standpoint of physiology, however, the proof offered by Hill and Flügge merely opens up a new problem. In the experiment which I have quoted from Hill's report, it is clear that the ill effects experienced by the men in the small chamber were not due to a rise of

body temperature, but merely to a high skin temperature. Quick relief was experienced when the electric fans were turned on and the air in the chamber was set whirling, and yet at the same time the temperature in the chamber continued to rise and the wet and dry bulb thermometers showed a difference of only 4°. I do not know how satisfactory the hypothesis which I am going to lay before you may appear, but to me it seems perfectly evident that the effects experienced by Hill and his pupils in that chamber were not the direct result of skin conditions, but rather the result of some process in the lungs as yet dimly understood, which is influenced by skin conditions. In this connection I would remind you that Bohr,[4] whose recent lamented death has removed one of the ablest investigators in this field, devoted nearly the whole of his working life to the attempt to prove that the passage of gases, and particularly the passage of oxygen, from the lungs into the blood is not a mere process of diffusion, but involves a distinct secretory activity by the pulmonary epithelium. This view, it is true, seems to-day to be further from acceptance than at the time Bohr died. Speaking for myself, I may say that, up to a short time ago, I regarded it with entire scepticism.

During the summer of 1911, it was my good fortune to take part in an expedition which spent five weeks on the summit of Pike's Peak.[5] There, under almost ideal conditions for the scientific investigation of the effects of low barometric pressure upon man and under the inspiration also of continuous association with Dr. J. S. Haldane, of Oxford, I was forced to the conclusion that Bohr had been upon the track of a great scientific truth. Much of the previous work of Haldane and his collaborators had tended to support the view of Bohr regarding the activity of the lung epithelium. The results of our observations on Pike's Peak, both upon ourselves and upon others, under a barometric condition of only 450 millimeters of mercury, seemed susceptible of no other explanation than that of pulmonary activity. The results of our investigations will soon be in print and available to those interested. I shall lay stress, therefore, upon only a few points. These are, that the symptoms of mountain sickness are in nearly all essential points the same, or closely similar to, the effects of bad ventilation. Mountain sickness, however, is not due to any skin effect, but is wholly due to an insufficient supply of oxygen to the tissues because of the low air pressure. In a newcomer on Pike's Peak the lips are blue, the temper uncertain; headache, nausea, vomiting, and even fainting are common. After four or five days, however, a healthy subject becomes adjusted to the low barometric pressure so that these symptoms disappear, and an ordinary condition of health returns. Our experiments indicated clearly that the principal reason for this return to health lies in the development on the part of the lungs of the power to secrete oxygen actively from the air of the lungs into the blood. It was very noticeable that in newcomers on the

Peak even a few minutes in a room, not excessively close to the senses of a regular inhabitant, was sufficient to precipitate an attack of acute mountain sickness. If such persons went outside in the cool and breezy open air, the attack was often relieved or prevented. The chill to the skin stimulated the lungs to secrete.

In the earlier work of Haldane and some of his collaborators there are a number of facts which suggest that one of the effects of cold upon the skin is to stimulate the pulmonary epithelium to secretory activity. Taking all of these facts into account, it is logical to conclude that the lungs are normally the seat of a more or less active process of oxygen secretion, and that the effects of warm moist air upon the skin are to inhibit this process in the lungs. In a sense, such an explanation brings us back to the point from which we started, namely, to the idea that in a close and crowded room the body is insufficiently supplied with oxygen; but this insufficient supply, according to the explanation which I have stated, is due not to an insufficiency of the oxygen in the air, but to an inhibition (probably by a hormone) of the power of the lungs to utilize this oxygen.

Lack of time prevents my discussing this topic in detail. The subject needs investigation along new experimental lines rather than a rehearsal of old data. Reference should be made, however, to the recent paper of Douglas and Haldane[6] on "the causes of absorption of oxygen by the lungs," in which improved methods are described and the secretory theory strongly supported. It is also to the point to mention certain evidence along an entirely distinct line which I have been collecting for several years past and hope soon to publish. My experiments show as clearly as vivisectional methods can that, contrary to the calculations of Zuntz[7] and of Krogh,[8] the blood stream is insufficient to transport all of the oxygen taken up by the lungs during vigorous physical exercise. The conclusion seems to be inevitable that Bohr was correct when he claimed that under certain conditions a considerable utilization, or at least disappearance, of oxygen occurs in the lungs—a pulmonary combustion, so to speak.

Along these lines, it seems to me, and along these lines alone, there appears to be hope of reaching an adequate explanation of the ill effects of bad ventilation and the stimulating influences of fresh air.

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[1] Rosenau and Amoss; Journ. Med. Research, 1911, XXV, p. 35.

[2] Flügge, Zeitschr. f. Hygiene, 1905, XLIX, p. 363.

[3] L. Hill, Journ. Physiol., 1910, XLI, p. 3.

[4] Bohr. Skand. Arch. Physiol., 1909, XXII, p. 228.

[5] Report of expedition to Pike's Peak (soon to appear in Phil. Trans. Royal Soc.).

[6] Douglas and Haldane, Journ. Physiol., 1912, XLIV, p. 305.

[7] Zuntz, Zeitschr. f. klin. Med., 1912, LXXIV, h. 3 and 4.

[8] Krogh, Skand. Arch. Physiol., 1912, XXVII, pp. 126 and 227.

For recent reviews of literature, see Crowder, Arch. Intern. Med., 1911, p. 85; and Sewall, Journ. A. M. A., 1912, LVIII, p. 174.

DISCUSSION.

Prof. VAUGHAN: Rosenau and Anderson some years ago showed that individuals suffering from asthma are unfit for injections of horse serum. People may become susceptible to horse protein by the inhalation of horsehairs, which may convey horse protein enough to sensitize. It will be interesting to determine whether animals sensitized to horse protein may sensitize other animals to the same protein through the expired air. Possibly something may be learned by injecting the fluid obtained from the expired air into human beings.

Prof. HOUGH: In a paper read three years ago, before the American Public Health Association, I urged the view that we should probably distinguish between the immediate or acute effects of poor ventilation and the effects which result from long exposure to vitiated air. Personally, I must still think that the acute effects are largely, if not entirely, explained by the physical conditions of high temperature, humidity, and absence of air movement. The subjective feelings are the same on a warm, muggy day in summer, and in a poorly ventilated room. Restore ideal atmospheric conditions as to temperature, moisture, and draught, and the symptoms disappear, even though the vitiation of the air is not removed. In any case, the practical solution of the problem of ventilation must involve, first of all, the maintenance of proper climatic conditions.

DIE BEDEUTUNG DER NÄHRSALZE, FÜR GESUNDE UND KRANKE.

Dr. RICHARD PETERS, Spezialarzt für Blut- und Stoffwechselkrankheiten, in Hannover.

Die Bedeutung der Mineralstoffe und ihrer Verbindungen für die Ernährung erforscht und sicher gestellt zu haben, ist ein Verdienst der neueren biologischen Forschung. Allerdings wäre es ungerecht, bei Anerkennung dieser Tatsache die verdienstlichen Vorarbeiten Liebigs und seiner unmittelbaren Nachfolger zu übersehen. Es lässt sich nicht leugnen, dass J. von Liebig bei seinen Erörterungen über die Nahrungsstoffe stets auch die Bedeutung der Salze in der Nahrung hervorgehoben hat. Auch Carl Voit verkannte ihre Wichtigkeit durchaus nicht. Das geht aus den Sitzungsberichten der baierischen Akademie der Wissenschaften hervor, in denen Voit im Dezember 1869 über die Untersuchungen seines Schülers J. Forster berichtete. Diesem gebührt auch das Verdienst, den Namen "Nährsalze" zum ersten Male in seinen wissenschaftlichen Arbeiten gebraucht zu haben, die er im Jahre 1875 [1] veröffentlichte.

Merkwürdigerweise ist dann jahrzehntelang der Begriff der Nährsalze fast ganz aus der wissenschaftlichen Literatur verschwunden und die Salze wurden vielfach als ein mehr oder minder zweckloser Bestandteil der Nahrungsmittel angesehen. Später, als man ihre Bedeutung für den Aufbau einzelner Organe und Gewebe zwar erkannt hatte, fehlte es doch an Klarheit über die einzelnen Salzverbindungen.

Inzwischen drangen die Arbeiten eines Mannes ins Volk, der infolge seiner eigenartigen Stellungnahme zur wissenschaftlichen Medizin sich in den Kreisen der Fachgenossen nicht jene Beachtung zu sichern vermochte, die seine Feststellungen immerhin verdienten. Es ist der physiologische Chemiker Julius Hensel, der in seiner "Makrobiotik" die grosse Bedeutung der Mineralsalze für den Betrieb der Organismen bis auf die kleinsten Einzelheiten beschrieb und gleichzeitig den Grund zu einer Mineralstofftherapie legte, die von neueren Autoren in vollem Umfange bestätigt worden ist.

Julius Hensel war es auch, der zuerst auf die Mineralverarmung unserer Feld- und Gartenfrüchte hinwies, und daraus die Notwendigkeit folgerte, durch Zuführung entsprechender Salzgemische dem Nährsalzmangel besonders der vegetabilischen Nahrungsmittel zu begegnen. Jedenfalls gaben die Arbeiten Hensels, mögen sie auch nicht frei sein von veralteten Anschauungen und manchen Irrtümern, doch den Anstoss zur Fortsetzung wissenschaftlicher Forschungen auf dem von ihm beschrittenen Gebiet. Die Aerzte Schüssler und Lahmann haben sich bei ihren Arbeiten ebenso wie in der Praxis unverkennbar auf den inswischen Verstorbenen gestützt und seine Erfahrungen nutzbringend verwertet.

Hensel wurde in seiner Eigenschaft als Chemiker zunächst aufmerksam auf die Verschiedenheit der Aschenzusammensetzung der Sekrete und Exkrete des Organismus, über die damals die Kenntnisse noch recht lückenhaft waren. Heute ist uns allen der Mineralstoffgehalt menschlicher Ausscheidungen bekannt. Ebenso geläufig ist uns die grosse Verschiedenheit des Aschengehalts pathologischer Exkremente von denen Gesunder. Ury und Alexander haben diese Variabilität wissenschaftlich erforscht und die Ergebnisse ihrer Untersuchungen veröffentlicht.[2] Aber auch bei Gesunden bestehen erhebliche Differenzen, die lediglich auf die Art der Ernährung zurückgeführt werden müssen. Es sei hier nur an die Untersuchungen von Blauberg[3] und Grundzach erinnert, die ungeachtet einer anscheinend nicht ganz einwandfreien und ungleichmässigen Methodik dennoch zu ziemlich gleichen Resultaten gelangten.

Unsere Organe und Gewebe, ja die verschiedenen Zellen sind auf einen Gehalt an unorganischen Materialien in genau festgesetzten Mengenverhältnissen engewiesen, wenn sie zweckentsprechend arbeiten

sollen. Wissen wir doch, dass die Erhaltung bestimmter Teile auch bestimmte Modifikationen der Mineralien erfordert. Mit Bezug auf das Herz hat sie L. Hermann[4] mit Bestimmtheit nachgewiesen. Besonders dem Kali- und Kalziumzusatz wird neben dem Natrium bei gleichzeitiger Anwesenheit von Chlor entschiedene Bedeutung beigelegt.

Die Anwesenheit mineralischer Salze im Organismus unterliegt erwiesenermassen einer so strengen Gesetzmässigkeit, dass Hirth sogar von einer absoluten Regulation ester Ordnung spricht, weil es dafür keine Kompensation im Sinne Rosenbachs gibt. Für das Salz existiert so wenig wie für den Sauerstoff ein Ersatz unter den Nahrungsmitteln und Energiticis. Tiere wie Pflanzen sterben, wenn ihnen das Salz vollkommen entzogen wird. Den Beweis dafür lieferte der Versuch Forsters, dessen Tiere bei Fütterung mit möglichst salzfreien Gemengen nach kurzer Zeit eingingen. Auch Bunge vermochte durch den von ihm veranlassten Lunin'schen Versuch keineswegs die Förster'schen Feststellungen zu erschüttern und er erkennt ebenso wie alle andern Physiologen die Notwendigkeit des wachsenden kindlichen Organismus an, Salze beständig in der Nahrung aufzunehmen. Ja, er glaubt sogar, dass der kindliche Organismus davon oft zu wenig erhalte.

Nur für den arwachsenen Organismus hält der geistvolle Forscher mit verschiedenen andern Physiologen die Notwendigkeit der Salzaufnahme nicht in gleichem Masse für erwiesen. Indessen widerlegt er sich selbst durch das Zugeständnis, der erwachsene Organismus bedürfe der Salzzufuhr "zu gewissen Zeiten," vornehmlich beim Ersatz des Spermas und—bei den Frauen—zurzeit der Menstruation, Schwangerschaft und Laktation.

Dass auch der erwachsene Organismus unter der Salzentziehung leidet, haben—ganz abgesehen von den zahlreichen Tierexperimenten—die bekannten Versuche an den sogenannten Hungerkünstlern Cetti, Succi, und Breithaupt[5] erwiesen, bei denen sich erhebliche Veränderungen des Mineralstoffwechsels zeigten.

Allerdings sind die Salze in der Nahrung quantitativ und wahrscheinlich auch qualitativ für den wachsenden Organismus nicht die gleichen wie für den erwachsenen. Schon Forster wies darauf hin, dass ein Teil der Salze sich in fester Verbindung mit den Körpersubstanzen in den Organen und als notwendiger Bestandteil in den Säften und im Blute finde. Ein anderer Teil ist nach Forster einfach in den Säften gelöst. Die ersten seien die eigentlichen Körpersalze, die letzteren die im Ueberschuss eingeführten Salze, die, beim Zerfall und der Oxydation der verbrennlichen Stoffe im Körper frei werden oder in Verbindung mit deren Zersetzungsprodukten getreten sind.

Wahrscheinlich gehören die von Erwachsenen aufgenommenen Salze zum grössten Teil der zweiten Gruppe an, während beim kindlichen Organismus das Verhältnis umgekehrt ist.

Dass übrigens eine regelmässige Zufuhr von Salzen auch beim erwachsenen Organismus notwendig ist, wird nicht etwa nur durch ihr Vorhandensein in den Sekreten und Exkreten erwiesen, sondern weit mehr durch die Tatsache, dass es gelang, durch ihre erneute Zufuhr den Salzhungertod bei den Versuchstieren abzuwenden oder die bereits eingetretenen gesundheitsschädlichen Folgen des Salzmangels wieder auszugleichen. Auch die unbestreitbaren Erfolge, die die noch junge Mineralstofftherapie aufzuweisen hat, sind ein Beweis für die Notwendigkeit der Mineralsalze für den Betrieb der Organismen einerseits und für den Irrtum der weitverbreiten und in vielen Lehrbüchern ausgesprochenen Annahme, der relativ geringe Bedarf an Mineralstoffen werde durch die Nahrung des Menschen überreichlich gedeckt. Sehr zutreffend bemerken dazu Albu und Neuberg,[6] für den gesunden Menschen treffe das zu, darum bleibe er eben gesund. Aber es treten im Körper ebenso häufig Störungen ein, die von nicht geringerer Einwirkung auf den Ablauf der Lebensvorgänge sind als die negativen Bilanzen im Eiweiss-, Fett- und Kohlenhydratwechsel. Wär der Bedarf an Mineralstoffen immer genügend, dann würden keine Anomalien im Mineralstoffwechsel entstehen, deren es so zahlreich verschiedene und auch wohl schwere gibt."

Diese Ansicht ist von der experimentellen kritischen Forschung einwandfrei bestätigt worden. Wie gewisse Fälle von Stoffwechselanomalien auf Quantitätsstörungen der anorganischen Zufuhr zurückzuführen sind, so gibt es auch wieder andere, die als Folgen von Resorptions- und Assimilationsstörungen angesprochen werden müssen.

Zu den wichtigsten mineralischen Nahrungsstoffen gehört der Kalk; an Phosphorsäure und Kohlensäure und Cl gebunden, bildet er den wesentlichen Bestandteil der Knochen und des Skelettes, deren Solidifikation er bewirkt; ebenso begegnen wir ihm in allen übrigen Organen und Geweben, wenn auch nur in geringeren Prozentsätzen. Die Einwirkung des mit der Nahrung aufgenommenen Kalkes geschieht aber nicht direkt auf den Knochen, sondern der Kalk bildet ein Nähr- und Reizmittel für das Periost, das nun seinerseits bei normaler Funktion die Knochenentwickelung ermöglicht. Auch bei der Blutbildung und für die Gerinnung des Blutes und des Plasmas spielen die Kalksalze eine beachtenswerte Rolle; auch als Schutzmittel gegenüber Gewebsreizen treffen wir den Kalk an: als Kalkabsonderungen, wie z. B. verkalkte Tuberkelknoten, Ablagerungen

in entzündeten Lymphdrüsen; in der Wandung alter Abscesse, schliesslich auch als die Kalkkapseln der Trichinen in der Muskulatur.

Nach Bunge ist Kalk neben Eisen derjenige Mineralbestandteil, dessen Mangel in der Nahrung analytisch am meisten nachgewiesen ist; denn ausser der Kuhmilch sind die meisten Nahrungsmittel kalkarm. Besonders hoch ist das Kalbedürfnis schwangerer und stillender Frauen, da der Säugling mehr Ca braucht, als die Frau zumeist hergeben kann; das Skelettgewebe des Neugeborenen ist zum grossen Teil knorplich angelegt, enthält also fast keine Kalksalze; was sich aber in der Säuglingsperiode bildet, ist Knochengewebe, das nicht nur den Zuwachs des Skeletts zu leisten, sondern auch den Knorpel der Fötalzeit zu substituieren hat.

Bei pathologischen Zuständen, besonders bei denen chronischer Unterernährung zeigt sich eine erhöhte Kalkausscheidung im Harn, wie andererseits eine erhöhte Kalkretention bei der Arteriosclerose beobachtet wird; die Annahme, dass als pathogenetische Ursache ein Mangel der zur Bindung, resp. Lösung des Kalkes notwendigen Mineralien vorliegt, dürfte eine gewisse Berechtigung haben.

Auch in der vielumstrittenen Rhachitisfrage ist man zu dem Resultat gekommen: Die auslösende Ursache des Rhachitis liegt in einer Störung des Kalkstoffwechsels, durch die eine erhöhte Exkretion von Kalksalzen in den Darm stattfindet. Die rhachitischen Skelettveränderungen sind Folgeerscheinungen dieser allgemeinen Stoffwechselstörung, dadurch entstanden, dass bei gesteigerter Resorption, besonders des mineralischen Anteils des Knochengewebes, eine qualitativ oft auch quantitativ unzureichende Opposition stattfindet. Dass das Skelettsystem rhachitischer Kinder weniger Kalksalze enthält als das gesunder, ist notorisch.

Aehnlich liegen die Verhältnisse bei der Osteomalacie, die von den meisten Forschern als Stoffwechselerkrankung aufgefasst wird; sei es infolge Kalkarmut der Nahrung, durch mangelhafte Resorption des Kalkgehaltes der Nahrung durch verringerte Alkalescenz des Blutes infolge Aufnahme von Milchsäure etc. ins Blut, die man im Harn und in den Knochen Osteomalacischer antraf oder endlich infolge von Phosphorsäureanomalien. Dass der Kalkumsatz auch für das Nervensystem eine wesentliche Bedeutung hat, erhellt aus dem Ca-Gehalt der Grosshirnrinde, deren Reizbarkeit sich erhöht bei Verminderung der Kalkmenge.

Im engen Zusammenhang mit dem Kalk steht im Organismus das Magnesium; in keinem tierischen oder menschlichen Organe wird es ganz vermisst; dennoch ist sein Vorkommen nur gering (z. B. gegenüber dem Kalk wie 1:9) aber kaum weniger wichtig als chemisches Bindemittel. Magnesium findet sich reichlich in der quergestreiften Muskulatur und besonders in der grauen Substanz von Gehirn und

Rückenmark; es scheint besondere Beziehungen zu den Nukleinen zu besitzen, denn es findet sich auch reichlich im Sperma; als integrierender Bestandteil zeigt es sich ferner im Blut und in der Lymphe.

Die Resorption des Magnesiums erfolgt im Dünndarm, seine Ausscheidung zum grössten Teil durch den Harn, teils auf intermediärem Wege durch den Dickdarm. Bei dem erheblichen Einfluss, den das Magnesium auf das Zelleben hat, ist es als ein für den Organismus unumgänglich notwendiges, nicht zu entbehrendes Mineral anzusprechen.

Dass der Schwefel ein notwendiger Bestandteil der Nahrung ist, gilt besonders den Tierärzten als bekannte Tatsache; denn Tiere, welche nicht genügend Schwefel in der Nahrung erhalten, verlieren die Haare. Der Schwefelumsatz des menschlichen Körpers ist kein geringer; im Tage durchschnittlich 2.5 g Schwefelsäure. In besonders inniger Verbindung sehen wir den Schwefel mit dem Eiweissmolekül: Kein Eiweiss ohne Schwefel, also auch keine Zelle, kein Gewebe, kein Organ ohne Schwefel; reich an Schwefel sind namentlich die Epithelialgebilde: Für sie ist der Schwefel so typisch wie der Kalk für die Knochen. Welche eminente Bedeutung den Schwefel zuzumessen ist, geht aus seinem ständigen Vorkommen im Protoplasma hervor; wie er in seiner noch so geringfügigen Menge unentbehrlich ist für die vitalen Funktionen im Eiweiss, in der Zelle, so müssen auch geringfügige Schwefel-Bilanzstörungen im Eiweissmolekül schwere Konsequenzen nach sich ziehen. Die Wichtigkeit der Gegenwart schwefelsaurer Salze im Blute für die normale Verdauung, für Galle und Leber ist bekannt (Taurocholsaures Natron). Die Ausscheidung des Schwefels als Schwefelsäure durch Harn und Kot, sowie durch Zuwachs der Nägel und Haare, erfordert eine Ergänzung an Schwefel, die etwa einer Menge von 3.5 g Schwefelsäure entspricht (Hammarsten). Besonders bei jugendlichen Individuen ist der Schwefel-Umsatz ein relativ höherer, also auch das Bedürfnis nach schwefelhaltiger Nahrung grösser.

Das Eisen, das in einer Menge von etwa 4 g im Organismus vorhanden ist, spielt als Sauerstoffträger in der Zusammensetzung des Blutes eine wichtige Rolle; es ist besonders deswegen von hoher physiologischer Bedeutung, nicht nur weil es an dem Aufbau des Hämoglobins beteiligt ist, sondern auch wegen seines allgemeinen Einflusses auf die Ernährungsvorgänge in den Geweben aller Organismen; findet es sich doch sogar in der blutlosen Cornea; mit Recht kommt ihm die Bedeutung eines Nährstoffes zu.

In seiner Eigenschaft als Sauerstoffträger entfaltet das Eisen oxydatische Kräfte, d. h., es wirkt wie ein Katalysator, oxydierend ohne aber selbst oxydiert zu werden. Wenn auch die Wirkung des

Eisens als hämoglobinbildende ausser allem Zweifel steht, so ist doch die Art seiner Resorption noch immer nicht sicher festgestellt. Abderhalden konnte in kleinen Dosen eingeführtes anorganisches Eisen in der Darmwand und in den Lymphwegen nachweisen. Nach den zurzeit geltenden Anschauungen über den intermediären Stoffwechsel des Eisens gelangt es auf dem Wege des Pfortaderkreislaufes, Leber und Galle, in den Darm.

Von grösster Bedeutung sowohl für den wachsenden Organismus, als für den erwachsenen ist der Phosphor; an alkalische Erden gebunden, nimmt er lebhaften Anteil am Aufbau des Skelettes und ist in dieser Form meist auch in den übrigen Geweben enthalten. Ohne Phosphor ist Nervengewebe irgend welcher Art undenkbar; in ihm ist er als Glycerinphosphorsäure vorhanden, im Knochengewebe als phosphorsaurer Kalk; in beiden Fällen spielt er die Rolle des Baumaterials. Welchen Anteil er am Aufbau des Gewebes hat, geht daraus hervor, dass ein Säugling im ersten Lebensjahre etwa 50–60 g Phosphor ansetzt. In organischer Bindung kommt er vor in den Proteiden, dem Nuclein und Lecithin und in den sogenannten Phosphatiden; besonders auch in den drüsigen Organen: in Leber, Milz, Thymus. Durch die Phosphorstoffwechseluntersuchungen wissen wir, dass der Körper ganz besonders energisch den Phosphor zurückbehält; jede Störung in den quantitativen Verhältnissen des Phosphors muss, bei seiner Wichtigkeit für die Zellarbeit, von einschneidender Bedeutung für die Existenzfähigkeit der Zelle sein.

Natrium besonders in seiner Form als Chlornatrium bildet fast die Hälfte aller im Blutserum gelösten Salze; es ist also begreiflich, dass der Verlust dieser Salze im Organismus nicht ohne Rückschläge für die Gesundheit stattfinden kann. Eine der wesentlichsten Leistungen des Natriums in unserem Körper liegt in seiner Bindung der überschüssigen Säuren; er ist ein Regulator unserer Lebenstätigkeit. Die drüsigen Organe bedürfen zu ihrer normalen Funktion ebenfalls eines gewissen Natrongehaltes, der ihre sekretorische Tätigkeit beeinflusst; so wirkt Natrium-Chlorid-Zufuhr anregend auf die Magensaftsekretion, die Salzsäureabscheidung. Der Kochsalzgehalt des Blutes bleibt meist ein konstanter, denn durch zeitweise Retention des Natrium-Chlorid wahrt der Körper die Isotonie des Blutes.

Hauptsächlich finden wir das Kalium in den Formelementen jeglicher Art, den Zellen; als Kaliumphosphat bildet es den Hauptteil der Mineralien der roten Blutkörperchen und des Muskelfleisches, des Organeiweisses. Ebenso wie das Natrium wirkt auch das Kalium als Säureregulator im Blute und in den Säften; weiterhin stellen die Alkalien Transportmittel der Kohlensäure im Blute dar und wirken als Lösungs-Mittel vieler Eiweisskörper in den Gewebssäften; gerade

auf ihrer wasserentziehenden Wirkung beruht ihre antiseptische, konservierende Eigenschaft.

Die Kieselsäure, deren Bedeutung für den Gewebeaufbau lange Zeit unterschätzt wurde, findet sich namentlich im Bindegewebe, nach einigen Autoren (H. Schulz) auch in hohem Masse im embryonalen Bindegewebe des Nabelstranges, ferner im Epithelialgewebe und in der Linse; nach Kunkel auch stets im Pankreas; besonders hoch ist der Gehalt der Kieselsäure in den Haaren, hier beträgt er 40 Prozent.

Das Fluor nimmt Teil an der Bildung der Knochen und Zähne als Fluorkalcium; auch im Blut und in der Milch ist es vorhanden. Der Fluorgehalt in den genannten Organen ist zwar minimal (für Knochen und Zähne etwa 0.05 bis 0.10 Prozent) aber es hat innerhalb seiner Wirkungssphäre seine bestimmte physiologische Bedeutung.

Das Mangan steht dem Eisen chemisch sehr nahe, ist aber bisher im menschlichen Organismus nur in sehr geringen Mengen nachgewiesen worden; doch nimmt man wohl mit Recht an, dass es an der Arbeit der blutbereitenden Organe teilnimmt.

Wie sich der Physiologe die roten Blutkörperchen ohne Eisen, das Knochengerüst ohne Kalk, das Nervengewebe ohne Phosphor nicht zu denken vermag, so weiss er auch, dass quantitativ Veränderungen der Minerale und ihrer Verbindungen entsprechende Störungen in der Lebensstätigkeit der Zellen und Zellgruppen hervorrufen müssen. Unsere Organe empfinden jede quantitative Veränderung ihrer Bestandteile als Reize und sie antworten darauf je nach dem Masse der Reizintensität durch Veränderungen in ihrer Tätigkeit. Diese Erscheinungen, sowie die mannigfache Art der Reizreaktionen sind Ihnen aus der Praxis so sehr geläufig, dass es hier nur dieses Hinweises bedarf. Wichtig ist ja lediglich, dass ein Mangel an mineralischen Verbindungen stets auch eine Störung im Ablauf der Lebenstätigkeit der Gewebe und Organe im Gefolge hat.

Wir müssen deshalb auch die Mineralstoffe als Nahrungsmittel anerkennen und es geht nicht an, sie mit Voit und Bunge als Genussmittel anzusehen, die zur Erhaltung des Lebens zwar wertvoll sein können, dem Organismus aber keine Kräfte zuführen, wie die Eiweisskörper, Fette und Kohlehydrate. Unbedenklich dürfen wir sie mit Forster und Hensel als wirkliche Nährsalze betrachten, denn sie sind als Zell- und Gewebsbildner unentbehrliche Nahrungsbestandteile, deren geringer Bedarf ihre Wichtigkeit durchaus nicht zu vermindern vermag.

Indessen sind sie noch weit mehr, sie sind zugleich kraftvolle Energieträger, deren Wirken im Organismus dank der van t' Hoffschen "Theorie der Lösungen" messbar ist.

Während die Energie der Eiweisstoffe, Fette und Kohlehydrate, nach Kalorien bemessen, in Wärme umgesetzt wird, kommt die

Energie der Salzlösungen in Druck und Bewegungserscheinungen zur Geltung und kann in Atmosphärendruck angegeben werden. Die Gesetzmässigkeit der durch den osmotischen Druck der Salzlösungen im Organismus veranlassten Bewegungschwankungen lässt uns die Bedeutung der Salze in noch hellerem Lichte erscheinen.

Schichten wir auf eine Salzlösung reines Wasser, so finden wir sehr bald im ganzen Gefäss eine Salzlösung von gleicher Konzentration. Die Salzteilchen aus der Lösung sind nach oben in das Wasser abgewandert. Diese Bewegungsserscheinung—Diffusion genannt—tritt in veränderter Form auf, wenn wir Salzlösung und Wasser durch eine halbdurchlässige Wand trennen. Sofern diese Wand wohl für das Wasser, nicht aber auch für das Salz durchlässig ist, werden die Salzmoleküle, die das Bestreben haben, aus der Lösung ins Wasser zu wandern, auf die trennende Wand einen Druck ausüben, den man als osmotischen Druck der Lösung bezeichnet.

Nach den Gasgesetzen, die nach van t' Hoff's Theorie Geltung haben für den osmotischen Druck, lässt sich dieser berechnen und wir wissen, dass eine 1/10 prozentige Kochsalzlösung einen etwa hundertmal so starken Druck hat, wie eine gleiche Eiweisslösung. Daraus ergibt sich, dass fast der gesamte osmotische Druck einer Nahrung den in derselben enthaltenen Salzen zugeschrieben werden darf.

Die einschlägige Literatur gibt weiter darüber Aufschluss, dass die gleichen Energiemengen verschiedener Salzlösungen in sehr verschiedener Weise in Wirksamkeit treten können. Wie bereits angedeutet, kann die den Salzen innewohnende Energie sowohl in Bewegungs- wie auch in Druckerscheinungen sich äussern. Darüber entscheidet die Durchlässigkeit der trennenden Wand, die in den körperlichen Organen eine sehr verschiedene ist.

Sind in einer Lösung verschiedene Salze vorhanden, so wird bei der verschidenartigen Durchlässigkeit der einzelnen Gewebswände der osmotische Druck sich an verschiedenen Stellen auch verschiedenartig äussern; anders im Magen, anders auch in den einzelnen Partien des Darmtraktus. Aber es kommen nicht nur die Partialdrucke der einzelnen Salze in Frage, sondern auch der Partialdruck der Dissociationsprodukte der Salze, der freien Ionen.

Diese Erscheinungen geben eine Erklärung der Tätigkeit der Salzverbindungen, sie erweisen aber zugleich auch die Unentbehrlichkeit jener Verbindungen für den Verdauungsvorgang. Es lässt sich verstehen, dass der Salzhungertod bei den Forster'schen Versuchstieren ebenso wie bei den späteren Experimentierobjekten nicht nur durch Mangel an Aufbau- und Neubildungsmaterial der Gewebe eingetreten sein muss, sondern zugleich auch mangels der notwendigen Druck- und Bewegungsvorgänge.

Indessen ist die Wirkung der Salze und ihrer Verbindungen auch damit noch nicht beendet. Sie wirken, wie die neuere Biologie lehrt, in gelöstem Zustande auch zugleich als Elektrolyten.

Dass elektrochemische Vorgänge in der Biologie eine wesentliche Rolle spielen, ist bekannt. Hier haben die Forschungen von Loeb, Hamburger, Koranyi, Köppe, Pauli und Anderen bereits grosse Klarheit geschaffen. Es würde zu weit führen, wollte ich auf die reichhaltige Literatur auch nur andeutend eingehen. Prof. Ostwald hat das in übersichtlicher und instruktiver Weise besonders in seinem "Grundriss der Allgemeinen Chemie"[7] getan. Neuerdings ist der Lehre vom elektrochemischen Betrieb der Organismen und dem elektrolytischen Kreislauf in Georg Hirth ein energischer Verfechter entstanden und es mehren sich die Stimmen, die seine Begründung acceptieren. Seine Ausführungen[8] gipfeln in dem Leitsatze, dass die Dynamik im organischen Betriebe nicht nur durch das Zusammenwirken der chemischen mit physikalischen Kräften ermöglicht wird, sondern dass diese letzteren wesentlich elektrolytische sind. Mit überzeugender Schärfe begründet er seine Ausführungen, wonach die Lösung der Salze im Blute nicht der Endzweck, sondern nur die Vorbedingung für die Erreichung des Hauptzweckes ist: als wirklicher Elektrolyt in die Nervenzellen und Leitungsbahnen überzutreten. Der Nachweis ist—wie bereits betont—nicht neu, auch Rosenbach hat ihn bereits geführt. Aber Hirth zeigt auch die Unentbehrlichkeit eines optimalen elektrolytischen Kreislaufes für alle Organe, um sie vor Störungen ihres Betriebes zu bewahren. Die Salze gewinnen unter diesem Gesichtspunkt eine geradezu souveräne Bedeutung für die prophylaktische Hygiene ebenso wie für die Therapie und es ist die Tatsache nicht uninteressant, dass neuerdings in den Kriegsministerien verschiedener Staaten die Frage der Salzversorgung (Kochsalz mit minimalen Zusätzen von Kalzium und Kalium) des manövrierenden und marschierenden Militärs zur Vermeidung des Sonnenstichs und der Brechruhr angeregt worden ist. Auch der Pharmakologe Hugo Schulz[9] Greifswald hat auf die vielseitige therapeutische Wirkung unorganischer Verbindungen seit Jahren hingewiesen.

Wir werden es nach diesen Darlegungen verstehen können, wenn Albu und Neuberg[10] das gesamte Wissen der Gegenwart über die physiologische Bedeutung der Salze im Organismus dahin zusammenfassen, dass sie—

(1) Zell- und Gewebsbildner und am Aufbau, Wachstum und an der Neubildung der Gewebe des Organismus beteiligt sind.

(2) Die osmotische Spannung in den Zellen und Geweben, im Blut und Säften vermitteln und Energieträger sind.

(3) Die Reaktion des Blutes und der Gewebssäfte, sowie den Ablauf vieler Fermentwirkungen, besonders im Verdauungskanal regulieren.

(4) Als "Katalysatoren" für eine Reihe chemischer Vorgänge wirken.

(5) Vermittler der im lebenden Protoplasma ununterbrochen ablaufenden autochthonen Vergiftungs- und Entgiftungsprozesse sind.

(6) Richtung gebend in die Zersetzung und Assimilation der organischen Substanzen eingreifen, somit tatsächlich, wie dies Hensel vor Jahrzehnten bereits erkannte, von geradezu lebenswichtiger Bedeutung sind. Ihre Zuführung darf daher in keiner Entwickelungsphase eine Unterbrechung erleiden. Sie bilden neben Licht und Luft den wichtigsten Lebenserhalter und niemand wird der Dreiheit Sonne-Sauerstoff-Salze den ersten Platz in der Hygiene und Therapie streitig machen dürfen.

Der Einwand nun, dass durch die übliche Nahrungsaufnahme das Salzbedürfnis in jedem Falle hinreichend gedeckt werde, wird durch die Erfahrung widerlegt. Bei vorwiegend vegetabilischer Ernährung tritt das Salzbedürfnis besonders stark hervor, wie der Salzhunger aller Pflanzenfresser beweist. Es sei nur an die Salzlecke der Rinder und Pferde und an die Wanderungen wildlebender Tiere zu Salzquellen im Wasser und Gestein erinnert. Für weite Volkskreise aber bildet das salzreiche Fleisch nur eine oft recht seltene Zuspeise, salzarme Vegetabilien die Hauptnahrung.

Ist es nun auch noch erwiesen, dass unsere Feld- und Gartenfrüchte infolge der Mineralsalzarmut des durch tausendjährige Kultur ausgelaugten Bodens ärmer an Nährsalzen sind als Früchte, die jungfräulichem Boden entstammen—und diese Tatsache wird von autoritativer Seite zugestanden—so wird die Widerstandsunfähigkeit und Lebensschwäche weiter Volkskreise erklärlich, die ungeachtet reichlicher Eiweiss-, Fett- und Kohlehydrateaufnahme an sogenannter Unterernährung leiden. Die logische Konsequenz dieser Erkenntnis ist systematische Zuführung der fehlenden Salzverbindungen. Kochsalz allein kann auf die Dauer unmöglich genügen, wenn auch dem Chlornatrium die erste Stellung unter den Salzen zuerkannt werden muss.

Aufgabe der wissenschaftlichen Forschung wird es sein, das Verhältnis der übrigen Salzverbindungen für die rationelle Ernährung der verschiedenen Lebensalter unter Berücksichtigung der sonstigen Lebensverhältnisse festzustellen, wie dies Julius Hensel schon früher mit nicht zu leugnendem Erfolge versucht hat. Immerhin bietet sich hier der exakten wissenschaftlichen Forschung noch ein weites Feld. In der Hygiene werden wir auf den Zusatz fehlender Salzverbindungen zu den Nahrungsmitteln nicht verzichten können und eine

Erweiterung der diätetischen Therapie im Sinne einer entsprechend dosierten Nährsalzzufuhr bei verschiedenen pathologischen Zuständen, die sich den bisher geübten therapeutischen Massnahmen wenig zugänglich erwiesen, ergibt sich dann von selbst.

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FRIDAY MORNING, SEPTEMBER 27, 1912.

DER EINFLUSS DER BEWEGUNG AUF DAS NERVENSYSTEM.

Prof. Dr. LEON ASHER, Professor of Physiology, University of Bern, Switzerland.

Es ist das Nervensystem, welches alle unsere Bewegungen beherrscht, und daher liegt der Einfluss des Nervensystems auf die Bewegungen klar zu Tage. Schwieriger liegen die Verhältnisse, wenn es sich darum handelt, umgekehrt den Einfluss der Bewegung auf das Nervensystem festzustellen. Ja, es könnte die Frage aufgeworfen werden, ob man überhaupt einen solchen Einfluss als einen wirksamen Factor ansehen dürfe.

Glücklicherweise giebt es ein absolut sicheres Fundament, von welchem die Betrachtung dieses Einflusses ihren Ausgang nehmen kann und das ist eine anatomische Thatsache. Die willkürlichen Muskeln, mit denen wir unsere Bewegungen ausführen, sind reichlich mit Nerven versehen, welche aus den hinteren Wurzeln stammen und morphologisch durchaus als sensible oder richtiger centripetale Nervenfasern bezeichnet werden müssen. Wie bekannt, hat sich Sherrington grosse Verdienste um die Aufklärung der sensiblen Innervation der Muskeln erworben. Nicht weniger sicher als diese anatomische Thatsache und für unser Problem noch bedeutsamer ist der Nachweis, dass diese Fasern sehr wesentlich an der Regulation der Bewegungen beteiligt sind. In einer grossen Reihe glänzender Untersuchungen hat Sherrington gezeigt, dass durch die Bewegungen des Muskels die in ihm liegenden centripetalen Nerven gereizt werden und dass die hierdurch enstehenden Erregungen—Sherrington bezeichnet sie als proprio rezeptive—den weiteren Ablauf einer andererseits ausgelösten Bewegung massgebend beeinflussen. Den Arbeiten Sherrington's haben sich gute Untersuchungen von Magnus angeschlossen, welcher gleichfalls die grosse Bedeutung der aus Muskelnervenerregung stammenden Componente für die Bewegung demonstriren konnte. Gewissermassen konnte der Ausfall einer Bewegung, z. B. ob eine Beugung oder Streckung eintreten würde, durch eine voraufgegangene Bewegung, die das betreffende Glied in eine bestimmte Lage brachte, geradezu vorausgesagt werden. Der Beweis dass es die Buskelnerven waren, welche den Einfluss ausübten, wurde dadurch erbracht, dass die Regulationen wegfielen, wenn

vorher die vom Muskel stammenden centripetalen Nerven in ihrer Verbindung mit dem Centralnervensystem unterbrochen worden waren. Alle diese Versuche betreffen zwar nur Rückenmarksreflexe; es kann aber kaum bezweifelt werden, dass es sich hier um ein für das ganze Centralnervensystem gültiges Phaenomen handelt. Dies um so weniger, als die originellen Forschungen von Uexküll's, an wirbellosen Thieren uns darüber belehrt haben, das ein Prinzip von allgemeiner biologischer Bedeutung vorliegt. Nach ihm ist, bildlich gesprochen, die Muskulatur im Centralnervensystem durch einen Repräsentanten vertreten und dieser Repräsentant sorgt dafür, dass die Bewegungsimpulse, welche das Centralnervensystem aussendet, den Bedürfnissen der peripheren Muskulatur entsprechen. Oder, um auf dem Boden der beobachtbaren Thatsachen zu bleiben, von Uexküll konnte zeigen, das je nach dem Zustand, in welchen er die periphere Muskulatur brachte entweder Erregung oder Hemmung dieses Muskels durch Vermittlung des Zentralnervensystems entstand. Nun ist eine derartige Beziehung nicht anders möglich, als dadurch, dass sensible, von der Muskulatur ausgehende Impulse in den Mechanismus des Zentralnervensystems eingreifen. Man kann sich hierüber verschiedene Bilder machen.

Alle diese Thatsachen, welche ich nur kurz skizzieren konnte, schaffen eine sichere Grundlage für die Betrachtung des etwaigen Einflusses der Bewegung auf das Nervensystem. Die Bewegungen, welche wir ausführen, müssen, dem gesagten zu Folge, die Nerven unserer Muckeln reizen, die Entstehung proprioreceptiver Reize veranlassen und dem Centralnervensystem einen Zustrom von Impulsen verschaffen, der nicht gleichgültig sein kann. Denn wo Einrichtungen vorhanden sind, um Erregungen aufzunehmen, ist der Sinn solcher Einrichtungen der, einem physiologischen Bedürfnis des Organismus zu genügen. Von diesem Standpunkt aus darf man behaupten, dass die Bewegung physiologischer Bedürfnisse auch die des Centralnervensystems erfüllt.

Die Analyse des Einflusses der Bewegung auf das Centralnervensystem ist vor die Aufgabe gestellt, von dieser Grundlage ausgehend etwas weiter vorzudringen. Die gewöhnliche Annahme, welche gemacht wird, ist die, dass durch Ausführung von Bewegungen das Centralnervensystem geübt wird. So richtig diese Annahme wohl ist, sie besagt nicht mehr als die Wiederholung einer oft gemachten Beobachtung. Worin diese Uebung besteht, ist eine Frage, welche sehr verschiedentlich und eigentlich nur in Gestalt von Hypothesen beantwortbar ist. Sehr häufig wird die Vorstellung vertreten, dass das Centralnervensystem durch Wiederholung von Bewegungen veranlasst werde, die Impulse zu diesen Bewegungen in zweckmässiger

und quantitativ mehr oekonomischer Weise auszusenden. Auch bedient man sich des Bildes, dass Innervationen, welche das Centralnervensystem häufiger aussendet, die Bahnen im Centralnervensystem "ausschleifen" helfen. Alle solche Vorstellungen berücksichtigen nur die centrifugale Seite des Geschehens. Sicher aber ist bei diesen Uebungserscheinungen das Centralnervensystem nicht ausschliesslich autonom dabei; sondern die peripheren ihnen zuströmenden Einflüsse spielen eine Rolle.

Am ehesten wird dies an passenden Beispielen klar. Die Gehbewegungen, die Ausführung feinerer Fertigkeiten wie Nähen, das Spielen eines musikalischen Instrumentes müssen erlernt werden. Unsere Aufmerksamkeit muss im Anfang fast jeder Einzelheit in diesen Bewegungen geschenkt werden; allmählich aber mit zunehmender Uebung bedarf es keiner Aufmerksamkeit mehr und die Bewegungen laufen in der sicheren, von höheren psychischen Zuständen uncontrollirter Art der Reflexe ab. Selbstverständlich sind viele Factoren am Werke, um die reflectorische Sicherheit gewollter Bewegungen einzuüben, untern anderen fortwährende Eindrücke unserer Sinnesorgane, je nach der Sphähre, innerhalb welcher sich die Bewegung abspielt. Es ist nicht meine Aufgabe auf diese Factoren einzugehen. Zu den Factoren gehören jedenfalls, nach den Voraussetzungen, welche ich entwickelt habe, die sensorischen Impulse, welche während der Ausführung der Bewegung selbstentstehen. Wenn man der Meinung ist, dass die vom Centralnervensystem ausgehenden Erregungen das Centralnervensystem so verwenden können, dass nachfolgende Erregungen leichter ablaufen und "abgeschliffene" Bahnen vorfinden, dann kann nichts der Annahme im Wege stehen, dass die genannten "proprioceptiven" Einflüsse das Centralnervensystem functionell formiren helfen. Bedenkt man wie gross der Einfluss der proprioceptiven Reize auf die reflectorischen Bewegungen ist, so wird man nicht umhin können, auch ihr Walten in den gewollten Bewegungen anzuerkennen. Die gewollten Bewegungen enthalten in den durch sie entstehenden proprioceptiven Reizen eine Componente, welche fortwährend auf das Centralnervensystem einzuwirken vermag und mithilft desselbe für die Bewegung einzuüben.

Versuchsweise möchte ich eine etwas in das Detail gehende Hypothese zur Discussion stellen, welche die Art und Weise betrifft, wie die Bewegung, die häufig ausgeführte Bewegung, ihren Einfluss auf das Centralnervensystem geltend macht. Ich glaube, dass wesentlich der Angriffspunkt im Rückenmark, jedenfalls subcortical liegt, und zwar auf der sensorischen Seite. Im Rückenmark oder subcortical dürfte er deshalb liegen, weil eben eingeübte Bewegungen ohne Beteiligung des höheren Sensoriums zu Stande kommen. Alle Geschicklichkeit unsrer Glieder ist ziemlich der intellectuellen Sphäre entrückt.

Ferner lehren Erfahrungen aus der Pathologie, dass gerade Schädigungen der sensorischen Gebiete des Rückenmarks zu auffallenden Störungen der Motilität führen, in viel höherem Grade als entsprechende Schädigungen im Grosshirn; die Tabes dorsalis mag als Beispiel dienen. Umgekehrt darf geschlossen werden, dass der Zustand der sensorischen Zone des Rückenmarks die motorische Leistungsfähigkeit mit bedingt. Nach dieser Richtung weisen ja auch die Aufschlüsse, welche wir Verworn und seinem Schüler über den Mechanismus der Strychninvergiftung verdanken. Je mehr wir Bewegungen bestimmter Art ausführen, um so öfter werden die sensorischen Apparate des Rückenmarks und vielleicht einige höheren subcorticalen gleicher Art durch proprioceptive Reize getroffen, so dass ein dauernd geänderter Zustand dieser Apparate entsteht. Sie werden gewissermassen abgestimmt auf die eingeübte Bewegung. Geringere Schwellenwerte der Reize sind fortan nur nötig, um den Ablauf der Bewegung, wenn erst der Impuls hierzu gegeben worden ist, so zu gestalten, wie es am zweckmässigsten ist.

Der naiven Anschauung der Laien nach hat die Bewegung mannigfache günstige Einflüsse auf das Nervensystem. Die wissenschaftliche Betrachtung darf ohne jede falsche Scheu diese naive Anschauung als einen leitenden Pfad benutzen. Das Nervensystem, welches selbst alle Teile unseres Organismus beherrscht ist durch eine planvolle Harmonie mit allen Teilen derartig in Wechselbeziehung, dass es auch in Abhängigkeit von ihnen steht. Daher kann es nicht Wunder nehmen, wenn die Bewegung, welche einen günstigen Einfluss auf den Kreislauf, auf die Atmung, auf die Stoffwechselprozesse ausübt, mittelbar dadurch auch das Nervensystem fördert. Dieser Einfluss darf durchaus nicht unterdrückt werden. Wenn wegen mangelnder körperlicher Betätigung die Atmung eine flache ist, der Kreislauf in den ungünstigen gelegenen Regionen des Körpers zu Stagnationen neigt, die Stoffwechselprozesse der Förderung durch den mächtigsten Impuls, der körperlichen Bewegung ermangeln, so entstehen Stockungen in der Elimination von Stoffwechselproducten aus den Geweben. Kein Gewebe ist aber empfindlicher als das Nervengewebe und es leidet in seinen feineren Functionen schon zu einer Zeit, wo die gewissenhafteste chemische Untersuchung, die gründlichste ärztliche Beobachtung keine positive Angabe zu Tage fördert. Es ist in den Lymphspalten, wo die für den Organismus schädlicheren Stoffwechselproducte sich anhäufen. Nun ist, wie bekannt, die Triebkraft, welche die Lymphe aus den Geweben entfernt eine recht geringe; die Muskelbewegung ist die bedeutsamste Hilfskraft; aus manchen Regionen fliesst die Lymphe überhaupt erst merklich ab, wenn die Muskeln in Aktion treten. Dieses Moment spielt eine Rolle unter den günstigen Einflüssen der Muskelbewegung auf das Nervensystem.

Während die bisher betrachtete Seite der Muskelbewegung we
sentlich dadurch wirkt, dass sie mechanisch zur Beseitigung vo
Stoffwechselproducten beiträgt, scheint dieselbe Muskelbewegung an
dererseits gerade durch Bildung gewisser Stoffwechselproducte ein
sehr grosse Bedeutung für das Wohlergehen des Nervensystems z
besitzen und zwar durch ihre Beziehung zum Schlaf. Es wäre müs
sig, über den Wert des Schlafes für das Nervensystem Worte z
verlieren. Gerade in unserer Zeit, die oft recht übertriebene Anforde
rungen an unser Nervensystem stellt, schätzt man dieses unentbehr
liche Sicherheitsventil nach Gebühr. Es ist bekannt, dass eine de
häufigsten Ursachen der Schlaflosigkeit oder des ungenügenden (na
mentlich in Bezug auf Intensität ungenügenden) Schlafes der Man
gel an körperlicher Bewegung ist. Leider ist unsere Kenntniss de
Schlafes noch recht gering. Die Beziehungen zwischen Schlaf un
körperlicher Bewegung können wir uns auf Grund all unserer bi
jetzt am meisten bewährten Anschaungen kaum anders erklären al
dadurch, dass die innerhalb physiologischer Grenzen sich haltend
körperliche Bewegung die Bildung von Stoffwechselproducten veran
lasst, welche das Zustandekommen des wohlthuenden Schlafes för
dern helfen.

Ganz beiläufig sei noch der Möglichkeit gedacht, dass durch di
Muskelthätigkeit Stoffwechselproducte, die ungünstig auf das Ner
vensystem wirken, in energischere Weise als ohne diese chemisch
beseitigt werden. An diese Möglichkeit zu denken regt z. B. di
Erfahrung an, welche man beim Diabetes mellitus macht. Durch
Muskelthätigkeit kommt es zu einer energischen Verbrennung de
Zuckers und seiner intermediären Abbauproducte, welche letztere
schädliche Wirkungen auf das Nervensystem entfalten.

Grosses Interesse knüpft sich an die Frage, in wie weit körperlich
Bewegung auf geistige Leistungen von Einfluss sein kann. Un
zweifelhaft giebt es gewisse geistige Bethätigungen, die eine so äus
serste Concentrirung der Gedanken verlangen, dass jede Art Ablen
kung störend empfunden wird. Die körperliche Bewegung an sich
und die begleitenden Nebenumstände dabei geben genügende Gele
genheiten zu solcher Ablenkung. Der Grad der Ablenkbarkeit is
individuell angesehen verschieden und es giebt viele Menschen
welche bei körperlicher Bewegung dasselbe an concentrierter Gedan
kenarbeit leisten, was andere nur bei ungestörter Stille zu thun ver
mögen. Es giebt aber geistige Leistungen, und nicht gerade di
schlechtesten, welchen die körperliche Bewegung darum mindesten
nicht unzuträglich ist, ja sogar direct förderlich. Jedem Gebildeten
wird in erster Linie die Erinnerung an die geschichtliche Ueberliefer
ung kommen, dass im klassischen Lande der angeregtesten und allge
meinsten geistigen Bethätigung, in Griechenland, der Unterricht in

den höchsten Dingen gern bei körperlicher Bewegung erteilt wurde. Ein so geistreiches und scharf beobachtendes Volk musste wohl gute Gründe haben, körperliche Bewegung und geistige Beschäftigung mit einander zu verknüpfen. Aus einer grossen Reihe cultureller Bedingungen heraus haben wir es aufgegeben dem Beispiele der Griechen zu folgen. Und doch kann derjenige, welcher aufmerksam die Biographie von Männern verfolgt, deren Leben erfolgreich der wissenschaftlichen Bethätigung, gelegentliche, sehr beobachtungswerte Äusserungen kennen lernen, welche ein helles Licht auf die Beziehungen zwischen geistigen Leistungen und der Bewegung werfen. Ich denke hierbei beispielsweise an eine äusserst characteristiche Bemerkung von H. von Helmholtz, welcher bekannte, dass ihm oft auf Spaziergängen urplötzlich die Einfälle der lange gesuchten Lösung schwieriger Probleme gekommen seien. Solche Beispiele aus der Werkstätte geistig thätiger Menschen liessen sich wohl viele häufen. Dürfen wir nicht Belehrung aus der auffallenden Thatsache ziehen, dass Gegenden, die ohne allzugrosse Mühe den Genuss der Natur erlauben, die bevorzugten Stätten sind, denen schöpferische Künstler entstammen oder in denen sie sich heimisch fühlen? Natürlich ist das ästhetische Moment ein schwerwiegender Factor hierbei, aber der Weg zu ihm ist die körperliche, mühelose Bewegung. Ich bin der Meinung, dass die körperliche Bewegung in diesem Sinne eine zwar noch nicht näher definirbare aber sicher vorhandene Wirkung auf das geistige Geschehen, demnach auf unser Nervensystem hat. Diese Seite unseres Problemes ist der ernsten Berücksichtigung durch die Erzieher unserer Jugend wert.

Die Sinnesorgane sind in gewisser Beziehung dem Nervensysteme zuzuzählen und deshalb sei noch auf eine mittelbare Wirkung der körperlichen Bewegung hingewiesen. Unsere Sinnesorgane schärfen sich durch Uebung und verkümmern durch mangelhaften Gebrauch. Für uns kommen wesentlich Auge und Ohr in Betracht, die beiden Erzieher des menschlichen Geistes. Wohl ist manches übertrieben, was von der feinen Schärfe des Auges und des Ohres bei Völkern behauptet wird, die in nicht sesshafter Kultur ein ungebundenes Leben der Freiheit führen. Man wird sich aber nicht des Eindrucks erwehren können, dass der Zwang Jahre lang in schlechter Haltung auf der Schulbank zu sitzen, ohne Compensation durch häufige Bewegung in der wirklich freien Natur, eine Versündigung an der Leistungsfähigkeit unseres Gesichtsinnes bedeutet. Von selbst sind demjenigen, welcher körperlicher Bewegung sich erfreuen kann, unzählige Gelegenheiten geboten, die von Nutzen für die verfeinerte Uebung unseres Sehorganes sind. Weniger offenbar ist der Zusammenhang zwischen Hörvermögen und den Leistungen unseres Ohres. Dem Stadtbewohner unserer Tage wird eher ein zuviel als ein zu-

wenig an Geräuschen aller Art geboten, so dass die Gefahr einer Abstumpfung bedenklich näher rückt. Die körperliche Bewegung als solche ist hier machtlos; nur mittelbar, wenn sie uns die ruhigere Natur aufsuchen lässt, gewinnt sie Einfluss.

Zum Schluss möchte ich darauf hinweisen, dass der Physiolog und Hygieniker keine körperliche Bewegung derjenigen an Wert gleichstellen kann, welche die natürliche ist. In unserer Zeit des Sportes, dessen emsiges Betreiben überal dort, wo er gesund ist, wir auf das lebhafteste begrüssen, erscheint mir eine Erinnerung hieran nicht unangebracht. Gleichmässige Uebung der Gesamtkörpermuskulatur und gleichmässige Beanspruchung, im Zusammenhange hiemit, der grossen Functionen unseres Körpers gewähren das Gehen und alle Beschäftigungen, die zu nicht überanstrengenden Excursionen veranlassen, sowie das Schwimmen. Der Sport in Ehren, aber die physiologischen Leistungen dürfen nicht in das Hintertreffen gerathen.

THE INFLUENCE OF EXERCISE ON THE HEART.

R. TAIT MCKENZIE, B. A., M. D., Professor of Physical Education, University of Pennsylvania, Philadelphia.

The hour has arrived for a complete reconsideration of the whole question of exercise in relation to the heart.

The invention of new instruments of precision, the compiling of statistics from large numbers of observations on the blood pressure, pulse rate, and heart sounds, in normal young people at rest and under exercise, have revealed the frequency of enlargements, variations, and irregularities, transient or functional in character for the most part, which might with propriety be termed variations within the normal rather than evidences of a pathological state.

Much medical opinion must of necessity be founded on the evidence of single or occasional cases, or even on that last refuge of the indefinite, "years of experience," which takes the place of accurate observation with so many men, and in consequence many a child is classed as diseased or defective and forbidden the exercise and play that is essential to its physical welfare, both present and future. James Mackenzie wisely says, "I have seen numbers of these going through elaborate methods whom I would have sent out to the play fields."

The mere presence of a heart murmur has been considered so serious and disabling a sympton that the necessary activity of many young people has been harmfully curtailed. Its importance in the field of cardiac symptoms has been grossly exaggerated, and too often the more grave and significant signs of heart weakness have been put too far into the background.

As the result of a conversation with Prof. Wenckebach, of Strassburg, in which he deplored the lack of accurate information as to the frequency of heart murmurs in different postures of the body and under conditions of rest and exercise in the normal youth, the following observations were taken at the University of Pennsylvania on the incoming class of students, whose ages lay between 17 and 25 years. In common with all well-regulated schools and colleges in America this university requires a thorough medical examination from all its students before beginning the course in physical education, which is an integral part of their college work. Out of the thousand and more who came up for this examination in October, only those were chosen who presented no apparent defect during the regular medical test. These selected men were given a more careful and thorough heart examination, and when any doubt was felt about the presence of a murmur, two, or sometimes three, observers made separate examinations.

The selected student took 50 steps of stationary running, raising the knees high at each step, so that the heart was brought to a state of great activity. He then lay down on a couch, then sat on a chair, and finally stood up, the stethoscope being applied in each position. For conducting the work and tabulating the results, I am glad to acknowledge with thanks the invaluable assistance of Dr. Ira Ayer. The report includes murmurs only. There were a few cases of arhythmia or accented aortic or pulmonary second sound without murmurs, but these have not been included; nor has note been made of any general conditions like anemia. Such cases were few, and the reporter wished to confine himself within the limits of his subject, viz. the frequency with which murmurs develop upon light exercise in individuals in whom no heart lesion is known to exist.

Murmurs that were doubtful have been included, and a few very faint ones that were evanescent were placed in that category. They have been classified according to location under six heads, viz: 1, apex; 2, apex and base; 3, fourth space just left of sternum; 4, pulmonic; 5, aortic; 6, aortic and pulmonic. They have been classified according to intensity into very faint, faint, moderate, and loud. The quality was in almost every case soft and blowing or puffing, although in a few cases the tone was slightly harsh.

Murmurs were found in 74 out of the 266 men examined (27.8 per cent); of these 35 were of the pure pulmonic systolic type, and if we include those in which it occurs in combination with others it was present in 64 cases, only 10 men out of 74 failing to show it.

Murmurs were much more frequent in the recumbent position. When they were audible in all three postures they were accentuated when the patient lay down and as the pulse became slower and stronger. This is not to be accounted for by the rotation in which

the examinations were made because the order was changed and reexaminations were frequently made to confirm their result. The following is the table of results:

Table of murmurs found in apparently normal health after exercise (50 steps, stationary running).

[E=Evanescent, B=Observed before exercise, V=Variable, U=Unclassified in strength.]

	Very faint.	Faint.	Moderate.	Loud.	Before.	Unclassified.	Total.
Apex:							
Lying		1 E.	1 B.		1 B.		
Standing							
Sitting							
Lying, standing, and sitting		1		1		2	7
Apex and base:							
Lying		1			1 B.		
Standing		1 E.					
Sitting							
Lying, standing, and sitting			1	1	3		8
Fourth space left of sternoid:							
Lying	2	3,1 E.	2		1	1 V.	
Standing					1		
Sitting							
Lying, standing, and sitting	1		3		2	1 E.	18
Pulmonic:							
Lying	1	4,1 E.	3,1 E.		2		
Standing					2		
Sitting	2 E.						
Lying, standing, and sitting	1	5	3		1 E.	9	35
Aortic:							
Lying							
Standing							
Sitting							
Lying, standing, and sitting			1		1		2
Aortic and pulmonic:							
Lying			1				
Standing					1		
Sitting							
Lying, standing, and sitting					1		3

No marked difference could be found between those who had led an active athletic life and those whose occupation had been sedentary, although the frequency seemed to incline to those of inactive habits rather than toward the more vigorous and athletic. The frequency with which these murmurs developed even on slight exertion (28 per cent) should, however, lead to caution in giving an unfavorable prognosis when they are found following severe strain or fatigue.

The disappearance of murmurs by change of posture alone is significant of their unreliability to determine the seriousness of a heart lesion when other symptoms are absent.

I have purposely given this investigation in detail because it shows how much variation within the normal may be found in this respect and also how fallacious may be the conclusions from an isolated case if unchecked by a series of similar observations.

Athletic exercises may be divided for our purpose into those in which a maximum effort or short series of efforts predominate, such as shot putting, weight lifting, heavy gymnastics, and sprinting; and

exercises of endurance in which the single effort is slight but the series prolonged to exhaustion, like walking, cross-country running, cycling.

Exercises of effort produce a sudden and rapid rise in blood pressure, 200 cubic centimeters and more, which rapidly falls when the effort is over. The pulse rate also returns quickly to its normal rate. The resiliency of the heart is tested by such exercises and they should be avoided by those of advancing years.

Exercises of endurance show a slower rise in pulse rate, and the blood pressure never rises very high, but even after the pulse has returned to its normal rate the pressure remains high, only returning slowly to the normal. The dangers of a continuous high blood pressure are more considerable in the young than that of a sudden rise, so that the long and exhausting tests of endurance seen in long races are not adapted to the best development of young and growing children.

These two forms of exercise are combined to a high degree in boat racing. In a 4-mile race a series of maximum efforts are continued for 20 minutes; the pulse increases its speed, the blood pressure rises. The first a feeling of exhilaration, is replaced by discomfort, followed rapidly by a sense of constriction and pain in the chest and head, anxiety, breathlessness, mental confusion, and, in extreme cases, fainting. The oarsman fights desperately for breath, the heart dilates widely as a matter of economy, the muscle working better when slightly stretched. This dilatation remains till the equilibrium is reestablished.

Murmurs always appear and slowly fade away; but even after the most severe strain one can seldom find any measurable injury in a week's time in a heart originally sound if the athlete has not passed 30.

It is in those of advancing years that the danger of these violent and prolonged efforts is seen. An elderly man, fresh from the office where he has been sitting for nine months, goes mountain climbing and at the end of a hard climb finds himself in great distress, a distress which does not disappear when he rests. His heart is found badly dilated and recovery is slow, if it ever takes place. Only too often the dilatation remains or recurs on the slightest exertion, and he remains a partial or complete invalid for the rest of his life. Cases have been reported of rupture of valves due to heavy and unexpected strains in men over 50, but I have found no record of such a case in the young.

Systematic exercise if kept within the limits of overstrain and exhaustion gradually builds up the heart in size and strength and even in most damaged hearts there is no better way of keeping up the tone and efficiency than by movements kept within the limit of fatigue.

Stokes pointed this out in Dublin, Oertel in Munich, and it h
been confirmed by many others. Graduated exercises are benefici
both in their immediate and in their remote effects, but controver
has raged fiercely over the remote effects of the more active and vi
lent exercise, and too often, opinion, prejudice for or against,
vague impression has taken the place of observation and facts.

The only statistics on which reliance can be placed show the fo
lowing results:

E. H. Morgan in his report on 294 old oarsmen found an increa
of two years in their expectation of life over the selected lives
Farr's English Life Tables.

George L. Meylan in his report on 152 Harvard oarsmen foun
an increase of 1.6 years, but his results were interfered with b
8 deaths in battle during the Civil War. Allowing them thei
allotted span the expectation would show an increase of 5.39 over th
selected lives of actuarial tables.

W. G. Anderson found that the graduates of Yale, who had wo
their "Y" on athletic teams, showed a mortality considerably les
than that of all other graduates.

Dr. Armstrong, of Wellington College, in 198 cross-country and
steeplechase runners finds, of the 13 deaths from 1870 to 1904, that
none died from heart conditions.

Hammett in his exhaustive compilation of distance runners found
similar results.

Blake and Larabee, in speaking of Marathon runners, after that
most exhausting of all athletic tests, write:

> So far as observed no permanent injury of any kind has resulted from any participation in these races.

Baruch and Savage, in their most thorough and painstaking obser-
vation on Marathon runners, come to the same conclusion, although
with more reservation.

It may be taken, as demonstrated then, that even severe athletic
competition does not appreciably damage the circulatory apparatus,
and its rôle in hastening the onset of arteriosclerosis is still difficult
to determine. Certainly it is not to athletics, but to the much more
strenuous occupations continued throughout long hours and under
unsanitary conditions—coal mining, iron working—that one must
look for information on this subject.

The exhaustion of continual overstrain in the young and growing
would of necessity be unfavorable to the child's best interests, but
even in them the recovery is so rapid and complete that one is aston-
ished at its thoroughness.

The body is constructed for a life of physical activity and the
heart needs constant and varied movement for its proper develop-

ment, and anything which curtails or prevents this natural means of growth must result in preventing the individual from reaching his highest possibilities.

DISCUSSION.

Dr. Louis F. Bishop, of New York: Every great heart specialist has rediscovered exercise as a most valuable remedy in heart disease. They have rediscovered it in England several times, and of late years in Germany. But in serious heart disease it requires courage to apply it, while from timidity the practitioner often induces degeneration of the heart muscle by compelling inactivity over too long periods.

Diet and out of door exercise are the only effective antidotes in very high pressure, and if any of you stop to think you will acknowledge that most terminal accidents in these people have happened when they were quiet in bed (thrombosis), and not when taking pleasurable exercise. Anger or sudden exertion may be followed by paralysis (hemorrhage). Most heart patients need a preliminary period of rest, but it is exercise that is reconstructive and causes their defective kidneys to work.

As to the young cardiopaths of which Dr. McKenzie has spoken, I confirm his experience, and one of the pleasantest things I do every year is to liberate some young people to lead natural lives at school. The polygraph is a great help in analysing these conditions.

CERTAIN ASPECTS OF THE INFLUENCE OF MUSCULAR EXERCISE UPON THE RESPIRATORY SYSTEM.

Theodore Hough, Professor of Physiology, University of Virginia.

No physiological effect of muscular activity is more immediate or striking than the increased breathing which accompanies it. Moderate work, such as a walk of 4 miles an hour, increases the respiratory exchanges three or four fold over those of complete relaxation, and vigorous work often increasese it tenfold; indeed, muscular activity is the one condition of normal life which demands distinctly greater work on the part of the respiratory system, and the latter responds to this demand with increase of functional activity comparable only with that produced by suffocation.

Furthermore, the effect of the augmented breathing is not limited to meeting the respiratory needs of the tissues. The increased thoracic aspiration is an important factor in the return of venous blood to the heart at a time when the diastolic filling of that organ must take place as rapidly as possible; nor is it a less important factor in the flow of lymph from extrathoracic to intrathoracic ves-

sels. The lymph flow, thus quickened from every organ of the body aids in the more rapid renewal of the interstitial lymph which forms the immediate environment of every living cell; the interchange of food and waste between capillary and cell is favored, thus partially if not largely, accounting for the "freshening" effects of muscular activity. It is also probable that this increased lymph flow may account for the leucocytosis which follows vigorous muscular activity; at any rate, it is significant that a similar leucocytosis follows breathing against inspiratory resistance, as in the use of a Kühn's breathing mask.

To be reckoned with also is the effect of the contractions of the diaphragm and abdominal muscles upon the organs of the peritoneal cavity. These contractions influence the circulation in the splanchnic area, relieving the congestions of sedentary life, and possibly exert a favorable massage action upon the organs in question.

Last among these secondary hygienic effects should be mentioned the fact that during muscular activity not only is the volume of air breathed increased, but all the lobes of the lungs are used. In this way, every part of the lung receives adequate ventilation and the mobility of all parts of the thoracic mechanism is maintained at a high degree of efficiency. The relation of this to the greater vulnerability of the apical lobes to tuberculosis can not be discussed here; but it is safe to say that while there may be a reasonable doubt whether the failure to ventilate these lobes is the sole factor concerned, there is nothing which justifies us in denying that it plays an important contributing rôle and hence should be classified as among the important probable hygienic effects of exercise.

The respiratory response to muscular activity, in meeting a very pressing need of the organism, therefore, favorably influences the circulation, the lymph flow, the environmental conditions of every living cell, the work of the abdominal organs, and probably aids in maintaining normal conditions in the lungs. Through this channel of respiration muscular activity exerts some of its most important hygienic effects on the body as a whole.

At the same time, with the more severe degrees of muscular activity, the increased action of the respiratory system is a response to a condition of pronounced physiological strain; and it is important to know as accurately as possible the condition of the organism indicated by this response. Let us, therefore, inquire what conditions are believed to influence, and especially to augment, the action of the respiratory center and which of these play a rôle in the response of the center to muscular activity. Factors augmenting the work of the center are: (1) Increase of the tension of carbon dioxid in arterial blood; (2) the presence of certain muscular metabolites in the

arterial blood; (3) rise of temperature of the blood going to the respiratory center; (4) deficiency of oxygen in the arterial blood, although this is negligible unless the arterial oxygen tension is approximately less than half the normal; (5) afferent nervous impulses, especially over the nerves of pain. To these may be added the possibility of influence from the lungs themselves, through the vagus nerves.

Of these possible factors the experiments of Geppert and Zuntz[1] exclude at once the action of nervous impulses from the working muscles and deficiency of oxygen in the arterial blood. These observers sectioned the spinal cord in the lower dorsal region, thereby removing from afferent connection with the central nervous system the muscles of the hind legs, which were then thrown into contraction by stimulation of the lumbar cord. The breathing movements were increased to approximately the same extent as by normal exercise, although the arterial blood proved to contain its full amount and presumably its normal tension of oxygen.[2] The same observers noted a marked fall of the carbon-dioxid content of the arterial blood, and concluded that excess of carbon dioxid in the blood going to the respiratory center could not be the cause of the increased breathing. The validity of this last conclusion has been called in question by Haldane and Priestley,[3] who justly point out that the carbon-dioxid content of the blood, as determined by Geppert and Zuntz, includes both the free carbon dioxid and that combined as bicarbonates or with proteins. Inasmuch as it is only the uncombined carbon dioxid which exerts a tension in the blood, and it is this tension of carbon dioxid which influences the respiratory center, it may well be that muscular activity diminishes the combined (and so the total) carbon dioxid without diminishing the uncombined, and, consequently, without diminishing the tension of this gas. It has been furthermore suggested that the acids produced during muscular activity may appropriate the bases of the blood and thereby lessen its carrying power for carbon dioxid; in this case there may be increased tension of carbon dioxid in the tissues (the respiratory center included) at the same time that the total quantity of this gas in the blood is diminished.

As a matter of fact, we have as yet no direct determinations of the tension of carbon dioxid in the arterial blood during muscular activity, nor have we any direct determinations of the "carrying power" of the blood for this gas under these conditions. Hence Haldane's suggestion, though plausible, must remain for the present an hypothesis awaiting verification.

In the absence of direct evidence as to the tensions of oxygen and carbon dioxid in the blood or in the respiratory center, the tensions of these gases in the alveoli of the lungs during muscular activity of

different degrees of intensity becomes of interest. Such have bee made by Douglas and Haldane, Pembrey and Cook, Hill and Flack and the writer of this paper.[4] I shall refer only to my own experi ments, as these are perhaps the most systematic yet made. Sample of alveolar air were collected representing four degrees of muscula activity, as follows: (1) During the sitting posture; (2) immediatel after a walk of 4 miles an hour; (3) immediately after a trot of 1 minutes, which produced marked hyperpnea but not labored breath ing; and (4) immediately after a hard run of 10 minutes, which pro duced decidedly labored respiration. Samples were similarly co lected at different intervals after the exercise. The results (averages are given in the accompanying table.

TABLE I.

	Alveolar tensions in millimeters mercury.	
	CO_2.	O_2.
Resting	37.0	100
Walk	39.5	103
Trot	39.7	104
Hard run (first 10 minutes)	35.0	113
Hard run (second 10 minutes)	29.4	118
2 to 5 minutes after hard run	25.9	126
7 to 10 minutes after hard run	28.5	112
15 to 20 minutes after hard run	26.0	113
30 to 40 minutes after hard run[1]	30.3	118

[1] One observation only.

For many details which appear on study of the individual experi ments reference must be made to the original paper. The table o averages here given shows in the first place a fairly close agreemen between the changes of alveolar tensions in the two gases; that is t say, as the carbon-dioxid tension falls, the oxygen tension rises. Th one exception to this is when the resting tension is compared wit that of the walk, and we shall see that this exception may be signifi cant. The general parallelism between the changes of alveolar ten sions of oxygen and of carbon dioxid, of course, suggests strongl an increased ventilation of the lungs as the cause. Taking as th basis of comparison the resting tension of carbon dioxid, the wal evidently causes a slight rise, the trot shows about the same tensio as the walk, or rather a tendency to a lower tension,[5] while with th hard run there is a distinct fall from that of the trot, this fall goin below the resting tension and increasing (doubtless to a certai limit) with the continuance of the run. In other words, whateve may be the condition of the blood, the increased breathing movement of hard muscular activity more than suffice to maintain the norma tensions of oxygen and carbon dioxid in the lungs. There is an over

s is of obvious advantage to the organ-
ference of pressure for both gases be-
coli when the greater speed of the blood
more rapid diffusion through the alveolar

condition of " overventilation " persists for
fter the cessation of the exercise, indicating
f the overventilation is one which is not imme-
the organism.

long ago concluded that the increased breathing
y is caused by the stimulating influence of some
lar activity other than carbon dioxid. These are
the blood and through that channel influence the
ter. They found that if the circulation through the
porarily stopped during the period of tetanizing the
no increased breathing results, even though the working
re still in nervous connection with the central nervous sys-
piration, on the other hand, immediately increased when,
ssation of the work, the circulation through the muscles was
blished, and this occurs whether the muscles are in nervous
ection with the central nervous system or not. These experi-
ts would seem to leave no doubt that the hypernea resulting from
the more severe forms of exercise is due to the stimulating effect upon
the respiratory center of katabolites, other than carbon dioxid, dis-
harged upon the blood by the working muscle. We may adopt this
conclusion without attempting to determine what these katabolites
are or how they influence the center. It is, however, a significant fact
that the duration of the condition of overventilation after the cessa-
tion of the work corresponds quite closely with the time that lactates
can be demonstrated in the circulating blood.

During the half hour or hour after the exercise, while the kata-
bolites are still in the blood and are influencing the respiratory cen-
ter, the alveolar tensions of carbon dioxid and of oxygen are probably
an approximate indication of the tension of the same gases in the
blood. If this be true, the blood must reach the tissues with an oxy-
gen tension between 10 and 20 per cent above normal and with a
carbon-dioxid tension from 20 to 40 per cent below normal. It would
lead us too far afield to consider the possible far-reaching effect of
this change in the blood; but the development of the conception of
the hormone action of carbon dioxid suggests the importance of in-
vestigation of the hygienic significance of this to the organism.

The facts thus far considered do not, however, justify the conclu-
sion that, in moderate exercise, such as a brisk walk, the stimulus to
increased respiration consists in the action of the muscular meta-
bolites in question. It will be remembered that such exercise shows,

not a fall, but a distinct rise of alveolar carbon-dioxid tension. This rise, it is true, does not seem at first sight very great; but the same rise, when produced in other ways in the resting individual, is capable of more than doubling the volume of air breathed. Hence it would seem to be an adequate cause. Moreover, if the muscular katabolites in question are lactic or other intermediate acids, we have every reason to believe that these arise because, under the conditions of intense work, the supply of oxygen to the working muscle is insufficient to effect complete oxidation to carbon dioxid and water. It may well be that moderate work does not overtax the power of the circulation to supply the oxygen needed for complete oxidation. In harmony with this line of thought is also the fact that moderate work is not followed by the low alveolar tension of carbon dioxid and the high tension of oxygen previously described for hard work and attributed to the presence of muscular katabolites in the blood; on the contrary, in this case the alveolar tensions promptly return to the normal. If this be true, the condition of the organism with moderate muscular activity differs not only in degree but also in kind from its condition during vigorous activity.

The study of alveolar tensions during muscular activity has led to a suggestion, by Pembrey and Cook,[7] which is deserving of attention, namely, that the respiratory distress which is relieved, on the continuance of the exercise, by the advent of "second wind," is due to a temporary excessive carbon-dioxid tension in the lungs and blood, and that "second wind" comes with the return of the carbon-dioxid tension to or below normal. The experiments of these investigators do not seem to the writer to be sufficiently extensive or controlled to establish the fact, but their results are highly suggestive and their theory should be tested by further experiment. Briefly, they found that during the period of respiratory distress at the beginning of the exercise the carbon-dioxid tension was often 25 per cent higher than normal; while, after the appearance of "second wind," it had returned almost or quite to the normal. It is one of the commonplaces of logic that the coincident occurrence of two events does not prove that they stand in any causal relation to each other; but the results of these workers are certainly suggestive.

Another important contribution to this subject has been made by Leonard Hill and his coworkers.[8] They have demonstrated the influence of breathing pure oxygen in lessening the severity of the respiratory distress during exercises of maximal effort, such as the hundred-yard dash. At first sight this may seem to be opposed to the view that "loss of wind" is due to excessive carbon-dioxid tension in the respiratory center, for the presence of a high tension of oxygen would not lessen the production of carbon dioxid. An explanation is, however, suggested by the very careful and important work of Lindhard,[9] who shows that with increasing tensions of oxygen the

sensitiveness of the center to the carbon-dioxid stimulus decreases. In other words, it may require a larger accumulation of carbon dioxid than normally to produce respiratory distress when the tension of oxygen in the blood is raised in this way.

In conclusion, I shall take the opportunity of suggesting a promising line of inquiry in this chapter of the hygienic physiology of muscular activity. There is evidence for the view that in regulating the ventilation of the lungs the respiratory center makes use of three variables in the act of breathing.[10] These are the rate of respiration, the amount of inspiratory effort, and the amount of active expiratory effort. Several students of the subject have drawn the conclusion that the rate and depth of respiration are controlled by different factors. The most important work on this subject is perhaps that of Scott,[11] who showed that, whereas in the intact rabbit dyspnea caused by breathing air comparatively rich in carbon dioxid involves an increase of both rate and depth of breathing, when both vagi nerves are cut there is an increase in depth but not in rate. With a slight modification I can state that the same thing is true of the dog. Richet also long ago called attention to the fact that the panting of dogs upon exposure to high temperatures consists of rapid and shallow respirations; and within the past year Nicolaides and Dontas[12] have shown that the polypnea resulting from rise of temperature of the blood does not occur if the connection of the respiratory center with the corpus striatum is broken. Rate and depth of respiration are thus controlled by different, although cooperating, mechanisms.

In addition to this, the writer is convinced that the depth of respiration seems to be similarly controlled by two factors, the extent of contraction of inspiratory muscles and the extent of contraction of expiratory muscles. In ordinary quiet breathing, the former is the more important; possibly it is the sole factor of depth. In labored breathing, active expiration becomes more and more pronounced. I have shown that, in the response to the dyspneic condition produced by breathing a confined volume of air, there are marked individual variations in the extent to which the expiratory muscles are used. Whether the same thing is true of the labored breathing of muscular activity, I am not able to state; but it is a priori probable, and, at any rate, is worthy of investigation. The largest efficient alveolar ventilation during labored breathing is secured by the active cooperation of inspiratory and expiratory muscles, and I would suggest that there may often be a failure of the expiratory mechanism to do its share of the work. This would place the individual at considerable disadvantage during labored breathing.

It seems worth while, therefore, for those interested in the physiology of muscular activity, and, especially, in its application to the actual work of physical training, to devise some method of testing (possibly as a part of anthropometrical physical examination) the respiratory response of the individual to muscular activity of different degrees of intensity, paying special attention to the three factors already mentioned and also to the relative part played by the lower and upper series of ribs. Such measurements may give important indications of the need of special training of the breathing in exercises of relatively great intensity.

In support of the view that such training is possible, I may cite an experience of my own when testing different individuals breathing a confined volume of air. Most of those subjects who had engaged in athletic work held down the rate until the later stages of dyspnea, securing their increased pulmonary ventilation by increasing the depth of respiration; and in this increase the expiratory muscles took an active part. A large percentage of those, on the other hand, who habitually took little exercise, would increase the rate from the first; in doing so, they did not allow time for full expiration, and these subjects suffered much more from insufficient alveolar ventilation than did the athletes. In the same group of subjects there were three accustomed to public speaking. Even though they had never had athletic training or experience, and took little exercise beyond walking, these three men responded to dyspneic conditions much as did the athletes. It seemed that they had grown accustomed to the use of the expiratory muscles in speaking, and the training of this mechanism showed itself in the more effective handling of the conditions of dyspnea.

Finally, I would raise the question whether in limiting our anthropometric measurements of the respiratory system to chest expansion, vital capacity, and force of expiratory effort, we are not content with too little; for these things alone do not indicate the dynamic condition of this mechanism. We should know not only its capacity, but also its actual behavior in response to the conditions of labored breathing. The solution of this problem in practice is not easy, but there is no reason to doubt that it is possible; and surely the maintenance of the best possible respiratory conditions in the organism under stress is an end worthy of any amount of patient, intelligent effort on the part of rational physical education to attain.

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[1] Geppert and Zuntz: Archiv für die gesammte Physiologie, 1888, XLII, p. 189.

[2] After this paper was prepared there appeared the work of Haldane (Journal of Physiology, 1912, XLIV, p. 305), from which he concludes that during muscular activity there is an active secretion of oxygen by the pulmonary epithelium from the alveoli into the blood, so that the arterial blood at this

time leaves the heart with an oxygen tension considerably above that of the air of the lungs. The correctness of this conclusion must stand or fall with the validity of the analytical methods employed.

[3] Haldane and Priestley: Journal of Physiology, 1905, XXXII, p. 225.

[4] Hough, American Journal of Physiology, 1912, XXX, p. 18. This paper gives full references to the literature of the subject.

[5] If, instead of using the averages, the "walking" and "trot" tensions are compared in each experiment where both were taken, it will be found that there is a slight fall of CO_2 tension in most cases.

[6] In these experiments the breathing movements are supposed to be unimpeded by fixation of the ribs in the muscular work; by nasal breathing, when this offers undue resistance to the entrance and exit of air; by fatigue of the muscles of respiration, when the work is unduly prolonged; or by any holding of the breath to give firmer point of origin to contracting muscles.

[7] Pembrey and Cook: Journal of Physiology, 1908, XXXVII, p. lxvii.

[8] Hill and Mackenzie: Journal of Physiology, 1910, XXXIX, p. xxxiii. Hill and Flack: Ibid., 1910, XL, p. 347.

[9] Lindhard: Journal of Physiology: 1911, XLII, p. 337.

[10] Hough: American Journal of Physiology, 1911, XXVIII, pp. 379–381.

[11] Scott: Journal of Physiology, 1908, XXXVII, p. 301.

[12] Nicolaides and Dontas: Arch. f. Physiol., 1911, p. 249.

PHYSICAL TRAINING IN THE UNITED STATES NAVAL SERVICE.

Dr. J. A. Murphy, Surgeon, United States Navy, United States Naval Academy, Annapolis, Md.

Exercise in the naval service may be considered in connection with its relation to the officer, to the enlisted man, to life on shore and afloat, to the variety available, to the work or play of the day, and to its effects, good or bad.

Until within a few years official recognition of the need of special forms of exercise has been limited more or less to the physical-exercise drills; sword, bayonet, physical drill with arms, and physical drill without arms. In the days of sailing ships, the enlisted force were generally active, well-developed men, obtaining frequent muscular exercise through force of circumstances, in lieu of which there must now be provided some scheme of compulsory physical training. Officers were also as a class of better physique, principally because the demand was less than the supply, so that selection, both mental and physical, was carried to a higher degree.

The modern navy has expanded rapidly, and conditions on shore and afloat have changed both from the hygienic and the physical standpoint. A great part of the crew now work below decks, in heated and doubtful atmospheres, motor power is replacing hand labor in boats and on shipboard, physical shore drills, like infantry and artillery, are of less importance than the necessity of perfect-

ing great gun drills in place aboard ship, while mental tension and responsibility is increasing with attendant drain on physical strength.

To compensate for the bad effect of these recognized altered conditions, executive authority has prescribed physical exercise for officers, and the Navy Department has encouraged athletics in many ways for the enlisted personnel. Failure to obtain satisfactory results comes from various causes. The physical drills soon become monotonous, consisting of the same series of movements day in and day out, while the basic principle of progressive uniform development is not present, through lack of some method by which weakness followed by improvement can be demonstrated. There is no special corps of instructors to keep alive the personal interest and to correct faults, the time allotted is short, and the system lacks command, so that control is soon lost, and the movements become perfunctory and spiritless.

The officers' walking test is better than nothing, but hardly sufficient to give the individual a daily work out of all his muscles or to improve the strength of his upper limbs and body. Athletics, being voluntary in character, only reach those who feel inclined to indulge, these few individuals among many being usually the well-developed physiques for whom one should ordinarily have no feeling of worry.

On shore, opportunity does not always exist for systematic exercise in the usual ways, most naval stations lacking a gymnasium or adequate area which can be devoted to voluntary physical training. Afloat, opportunity is still further restricted.

The peculiar conditions, not felt ordinarily in civil life, during the more or less lengthy periods of work under discipline and responsibility of varying degree, affect the personal inclination, the hours off duty being devoted to family or to pleasure of nonathletic type for the freedom and relaxation that goes therewith.

Unlike civilians, who, as a rule, remain in the same locality, the chances of naval men becoming active members of athletic organizations or clubs are slight, lack of example being a factor here.

Under the American system of making specialists out of a few individuals, the primary idea of exercise would seem to tend to the creation of a desire on the part of a few to excel in doing feats of skill and strength, and to the many a desire to view such displays, the rounding out, uniform, and healthful development of all individuals being a secondary instead of a primary consideration. It follows that for many individuals there is created no actual liking for exercise, these persons never having really felt the well-being that comes from a proper dosage, exercise for the athletes having been made a drudgery in order to obtain excellence in condition and team work, all pleasurable sensations being lost in the lust for conquest.

The athletes, therefore, unless they make their living thereby, soon give up their methods of obtaining exercise because of dislike or inability to gather others together for a contest or from lack of a field of play, while the nonathletes, having learned no other form of athletic pleasure than that of viewing others perform, go the way of the ignorant.

Observation of hundreds of applicants for enlistment or appointment in the service, particularly in the case of youthful candidates for midshipman at Annapolis, supposedly the selected of the land (many having passed through college or preparatory schools where opportunity for physical training at the present time is excellent), shows a most marked neglect of personal knowledge in the use and lack of results in the application of exercise to the improvement of defects in physique, these young men for the most part being flat-chested, round-shouldered, with head drooping and hips carried forward and spine distorted; unhealthy skins, poor circulation, and frail musculature often complete the picture. Of the few who are well developed many have exaggerated certain parts so as to have become defective in posture. Their muscles are reduced in range of movement from continually doing heavy work of the same character and from unequal development of antagonists, so that they are muscle bound, awkward, sluggish, and, when attempting to apply their power, fight the effort through lack of coordination.

These young men, both weak and strong alike, are all well grounded, however, in exercises commonly classed as sports, which, from the results, appear to be more popular through desire for fame, poor advice, or lack of restriction, than basic exercises which would have prepared the body by correction of its physical faults for the strains of effort.

At the United States Naval Academy, where, at the present time, physical training is considered of great importance, all forms of exercise, both voluntary and compulsory, are encouraged under certain restrictions of various kinds.

The assigned compulsory forms of exercise are made up of drills and athletics. The athletic drills being infantry, artillery (field pieces drawn by hand), great gun (using dummy bags and shell of same weight as standard charge), mines, seamanship (rowing and sailing boats), gymnasium, and sword. The compulsory athletic contests between classes, divisions, and companies, are rowing (cutter, three-fourths mile), tennis, gymnastics, wrestling, swimming, fencing handball, football, basket ball, baseball, lacrosse, and field and track.

The drills are both outdoor and indoor and, in addition to those regularly assigned as part of the academic course, others are assigned

as competitive. The compulsory athletic contests in the different seasons are restricted to individuals not members of the navy squads in each sport, so that there are very few of the total number of midshipmen who at some time are not engaged in athletics.

Voluntary lines of effort, in which the midshipmen engage for recreation, or collectively represent the institution against other colleges, are of the usual kind: Crew racing, football, basket ball, track and field, baseball, lacrosse, wrestling, swimming, gymnastics, tennis, fencing, golf, handball, walking, horseback riding, and bicycling.

In connection with the above, it might be noted that the aim of exercise should be to correct faulty posture or deformities; strengthen weak muscle groups; improve nervous control and coordination to obtain a quicker response to the will; improve the appetite, digestion, and absorption, thus improving metabolism so as to increase body weight (muscle) and burn up excess of food (fat); and to strengthen the heart and lungs; the body being placed in a position best adapted to meet the daily demands of life brought out by the strain of physical and mental activity.

The effect on physique of constant discipline; compulsory study hours; examinations; youth; natural ambition, frequently accentuated by reward for excellence; rivalry, urging of professional coaches and trainers, and desire for fame; is not always considered in conjunction with excessive physical exercise. These combined effects often lead to insidious overdoing, particularly when there is failure to remember that exercise should be recreational or developmental in character, when endurance is cultivated rather than skill and team work for short periods, and when the question of unnatural fatigue is lost sight of.

The primary object of the interclass drills and games is to stimulate an interest in the various exercises and to force as many individuals to engage in physical improvement as possible, the secondary object being to develop material for the first teams (this last is the predominant idea in the American scheme of physical training and is responsible for the poor results so far observed). Class contests are more in the nature of recreational strife, making the exercise one of play instead of work. There is no necessity for arduous training, due to the lessened speed and form expected from the contestants and to the fact that winning or losing is not a vital point, the players being able to conserve their strength by slowing up when fatigued.

In the development of teams for interinstitutional contests the peculiar mental state affecting coaches (due to thoughts of prestige or finance usually) and players (effect of esprit de corps), brought out by fear of losing, has usually evolved an excess of zeal, both on the part of those engaged in the various sports as well as in those

charged with the production of a winning combination. This mental state forces matters, there being no time for progression, and with failure to realize that shortness of season, lack of previous preparation, press of studies, relative immaturity, and effect of constant discipline may be exerting a drain on vitality, results are not always as expected. In the production of a winning team the professional coach is thinking very little of the future of his subject, but a great deal on obtaining what he terms "material," which really means the survival of the fittest. Commercialism is a strong factor in the athletics of to-day.

Certain sports have the endurance element prominently to the front, and it is frequently noticed that this element is counted on at times to cover lack of skill and team work. Ill effects are noted frequently, even in the well trained, from cumulative strain in endurance contests. This is not so true of exercises of speed and short duration, where only momentary after effects show, such effects being nullified by proper care and restriction.

In the naval service statistics proving that athletes live long are not of as much importance as proof that this type of individual will continue to withstand the marked mental and physical strain of modern naval life, which can be expected to increase in time of peace as well as in time of war. The same man in civil life might be considered a good risk both from the average business and efficiency standard, but this does not always hold in the service where responsibility is never ending, and on this point hinges statistical differences.

Some of the effects of overindulgence in athletics, commonly widely advertised as of benefit to the individual, are symptoms of acute exhaustion, breathlessness, rapid heart action, arythmia, cyanosis (dilatation of right heart), and collapse; later loss of weight, nervous and mental exhaustion, lack of quickness of thought, loss of muscle elasticity, dull and listless eyes, unhealthy skin, and general fatigue, necessitating going on the sick list to recover from autointoxication due to the circulation of waste combustive products within the body. Still later effects have been noted in those of athletic history in the naval service, conditions applicable to athletic strain affecting future usefulness. Statistics proving favorable longevity in the case of athletes are based on those who, as the survival of the fittest, handed their names down to posterity; included in the nonathletic class are the weak physiques and the near-athletes who failed to make the team, and these last are particularly more apt to demonstrate consequences, as experience shows that as a usual thing they failed because of lack of proper basic strength, many trying to emulate the strong, through lack of proper supervision, to their detriment.

Statistical comparison should be made between the athlete of robust physique and his nonathletic fellow of robust physique.

Realizing, from the standpoint of physique, and from observation, that conditions affecting physique of midshipmen were not perfect, a board of officers recently considered the subject, and the following facts were discussed and recommendations made accordingly:

Prior to the Spanish War officers were graduated physically superior to those now graduated, because the course then provided for the survival of the fittest, the weeding-out process beginning on entrance examination and continuing throughout the course. Candidates physically deficient were rarely admitted to the academy, while the pressure was such by reason of the fact that but 45 per cent of those entering graduated, that the physically weak who escaped the examining board, being unable to stand the pace, dropped out. Of the graduates, those at the head of each class in varying percentage only were commissioned, still further increasing the selection. At present about 3 per cent enter after rejection with gross physical defects, and 67½ per cent of those who enter graduate, most of the failures being due to professional causes. Many enter well below the weight and chest requirements, no other cause for rejection than general poor physique being applicable to this type. These last, if followed up, prove to be poor soil, and, in going over the records of 1,800 midshipmen, it was found that all those developing consumption in their future service came from this class (no midshipman above the physical requirements developing the disease); 85 per cent of those finally rejected physically (125) in the number mentioned were under weight and chest requirements on entrance.

In the old course, the summer practice cruises were of importance from the physical-training standpoint, owing to the constant making and furling of sail, pulling on ropes, and climbing of rigging in maneuvering ship on the sailing vessels used for instruction during the period. Such work in the open for more or less lengthy periods at sea was very beneficial, particularly in developing both muscular courage from going aloft, and the muscles attached to the upper limbs and chest, which compensated for the excessive leg development no doubt produced, then as now, by the hourly daily marching to and fro for considerable distances in the aggregate, necessitated by recitations, drills, and climbing of stairways in quarters and other buildings. This physical development is now lost on the present cruises, most of the course being devoted to mental effort. The practical exercises in various departments on shore, as the theoretical studies have enlarged in scope, have also become mental and no longer retain the physical element.

To offset the loss noted, little or nothing was done except to cultivate voluntary athletics, and this branch of physical training has evidently, by itself alone, failed to come up to expectations, principally because it reached only those, as a rule, for whom no concern should have been shown. In addition, it is a fact that the services of officers have been lost to the Government through overindulgence in athletics, fostered by overzealousness in applying effort toward demonstrating the acme of power and skill without restriction

In the Navy or Army no great advantage will accrue if a few individuals are capable of shining physically in certain lines of effort, this being of questionable benefit when the great mass is neglected, so that the speed of the whole depends on the slowest.

To obviate the harmful effects of overindulgence in athletics, the following restrictions are in force: Restriction of boxing to class instruction, championship contests being barred; restriction of contests as to number, duration, with lengthened interval between; restriction to but two lines of effort in one year, to prevent constant training; supervision on the field of play by a medical officer who has authority, independent of coaches, to prevent a contestant from playing, or to remove him from a game, this provision having reduced casualties and checked tendency to overwork; endurance contests, like distant track and crew racing, are considered harmful to midshipmen, contests of speed being favored as developing more headwork and but momentary rather than cumulative strain. The quarter-mile running race is now the limit in this line, while crew racing has still further been reduced in distance from 2 miles to $1\frac{5}{8}$ miles. More gymnasium developmental drill was recommended.

The strength test by muscle groups (49 in number) is used to separate the strong from the weak; those who fail to pass receive 60 hours' gymnasium work additional to the 16 hours now assigned regularly to all individuals during the winter months. All gymnasium drills are compulsory, there being no substitutions permitted, nor is any individual excused. The effect of the strength test is to bar the weak from taking part in strenuous athletics, so that the work of the coaches and trainers is no longer wasted by having unwieldy squads to handle, composed for the most part of unfit material. The athletes are further checked as to fitness by a separate yearly medical examination, and by other examinations during the season. The weaker men have a strong incentive to perfect themselves by reason of the extra drill and the inability to shine at play.

To prevent slouching, with consequent yielding in the spine, flat chest, and prominent abdomen (sway back), individuals are assigned extra drill for this defect, even if well developed.

Swimming is a necessary accomplishment, and failure to meet the requirements caused three of the first class of this year to fail to graduate with their fellows. An additional incentive toward showing an interest in this accomplishment is the extra drill periods assigned in recreation time, and the possibility of having to practice while more ambitious individuals are enjoying annual leave.

The restrictions noted have created a general interest in basic physical improvement, athletics being now secondary, which is the proper relation.

Gymnasium drills are no longer easy-going exercises, or imitative in character, such methods having been discarded because of the poor results obtained, and because of the ease with which shirking could be practiced. A modified form of the Swedish system has been found to lend itself very well to the training of physique, and this system is now in force, so that all exercises are in the nature of military movements under strict discipline and command. The results have been excellent (see article in United States Naval Institute, June, 1912) and are certain to continue so, because discipline can be enforced in the naval or military service.

The constant bombardment of consciousness by words of command, followed by instant action, is having an insidious influence in making the individual more responsive to strictly military orders, which is a desirable addition from the naval standpoint to good physique and muscular control.

Strong and weak are given a regular course of gymnasium work, because it has been found that the Swedish exercises prevent contractures of muscles, deficient range in joint movement, defects in posture, clumsy and sluggish response to various impulses of the will, and decreased coordination, all of which are apt to be present even in the strong.

In the general service conditions are similar to those applicable formerly to the midshipmen, and there is need for a method of compulsory exercise to overcome the present failure in results. The setting-up drill has failed to accomplish its purpose because of several faults; sameness; no insistence on form; lack of exercises requiring muscle and nervous control (muscle courage); and lack of military command to prevent monkeylike imitation; and indifferent, perfunctory, noncohesive response.

The enlisted man becomes often, after enlistment, well developed as a result of the work he is required to perform; much of this work is, however, heavy in type or automatic in character, there being no occasion to think of what is being done. The result is a ponderous, slouchy, negative strength, few of these individuals being able to use their muscles with any celerity or activity in movement.

There is need also for forms of exercise in the nature of feats, such as leaping or vaulting, not only to cultivate muscular judgment, but to momentarily increase the speed of the motor apparatus, heart, and lungs, to improve the endurance of the subject which, from his life at sea level, is nearly always defective.

Consideration is now being given to the question of adopting a form of compulsory physical drill at all shore stations and on board ship, to apply to nearly all officers and men, which will provide for a daily workout for all the muscles, provision being first made for a school of instruction, so as to obtain uniformity in method, and by a system of inspection prevent deterioration from lack of interest.

This system, if adopted, will probably be based on the Swedish method of physical training, because of the command element, the progression provided, and the type of apparatus called for, the last being of importance because most of it exists on board ship or can be easily improvised without calling for additional storage space.

THE PREVENTION OF ARTERIOSCLEROSIS AND HEART DISEASE IN OTHERWISE HEALTHY INDIVIDUALS PAST MIDDLE LIFE.

LOUIS FAUGERES BISHOP, A. M., M. D., Clinical Professor of Heart and Circulatory Diseases, Fordham University School of Medicine, New York City; physician to the Lincoln Hospital.

Every observing person whose experience extends past 40 knows that heart disease is constantly developing among his contemporaries who are otherwise healthy. Surprise is often expressed that this man or that, in spite of what seemed to be right living, has become a victim of heart disease.

The slightest consideration leads to the belief that there is some active hidden agent working to cause heart disease and hardening of the arteries, and a little examination shows that the causes are not those usually assigned. The healthy old drunkard disproves alcohol as a cause. Rheumatism more often attacks the young, and in later life generally spares the heart and blood vessels. Men who really overwork are not as numerous as is often thought, and worry, while a great cause of heart disease, is indirect in its effect.

The fact is constantly appearing in the literature of the day that circulatory disease as shown by statistics is more frequent than formerly. Tuberculosis has for its victims the most attractive of the youth of the land, but heart disease claims the best and most successful of those past middle life. Much attention is being directed to tuberculosis because its cause and progress have become matters of public knowledge. The victims of heart disease, however, still too

often go for months and years without intelligent treatment because no one has pointed out the danger signals and because the interest in germ disease has absorbed everyone's attention.

Heart disease and hardening of the arteries in nine times out of ten are, I believe, due to disturbances of the chemistry of the body. The prevention of heart disease and hardening of the arteries must be accomplished by a proper regulation of the chemistry of the body, particularly that pertaining to the intestines and the liver. This is accomplished through diet, rest, and exercise, through the administration of certain well-defined remedies, and the limitation of nervous strain, than which nothing is more potent to upset the bodily chemistry. The technical chemistry involved is difficult and complicated in the extreme, and entirely beyond the comprehension of those not specially trained in the chemistry of this particular branch of work.

The truth is not found in popular explanations with such such trite names as "intestinal fermentation," but is found in the ultimate chemistry of food substances and their changes in the human body.

The tendency to heart disease in otherwise healthy individuals past middle life can better be detected by a chemical examination of the urine than by an examination of the heart itself. By the time the heart itself shows poisoning, as appreciated by the sufferer on account of palpitation, pain, or shortness of breath, irretrievable damage has been done, and the chemical vice has become so deeply seated that an extreme regimen is necessary, while in the early stages a slight modification of diet and hygiene can check the trouble.

It is often remarked that the consumptive is fortunate who early in his disease has a severe hemorrhage that thoroughly convinces him of the necessity of treatment. In the beginning heart disease and hardening of the arteries, unfortunately, has no symptoms, and the changes in the organs themselves are such as can only be detected by the most expert examination. Fortunate is the individual if the disturbing chemistry of the body leads to pronounced suffering in the direction of recurrent headache, biliousness, or dyspepsia before the heart and blood vessels are damaged, because these things may lead to treatment and prevention.

The prevention of heart disease and arteriosclerosis in otherwise healthy individuals past middle life can only be accomplished infallibly when there is the periodic chemical examination of the bodily chemistry at stated intervals by an expert chemist and when early and proper courses of treatment counteract the tendency before damage is done.

Some of the large life-insurance companies are now examining for this underlying chemical cause of heart disease in otherwise healthy persons who apply for large policies, and yet one of the saddest ex-

amples that I ever witnessed of chemical damage to the heart and blood vessels was in the medical officer of one of these very companies.

I am bringing to you definite conclusions that are the result of work devoted exclusively to the practical care of heart patients, but I would urge upon my colleagues who are privileged to do laboratory research the vitally important bearing of their work upon the life and well-being of mankind at the most useful period of life.

The prevention of arteriosclerosis and heart disease in otherwise healthy individuals past middle life thus brings up a problem that is seldom considered.

However much constant observation may tend to the contrary, each individual considers himself immune to these diseases, so the victim of heart disease and arteriosclerosis seems to himself a special victim of providence.

So little is the prevention of arteriosclerosis and heart disease believed to be possible that in a congress such as this it has been seldom discussed, nor indeed does the topic seem to have occupied much the minds of medical men. I judge this because an extended experience in addressing medical bodies on this topic has shown that but few physicians have formulated any ideas as to the causation of cardiovascular disease, and hardly any have undertaken its prevention.

There are three conditions of the medical mind that are met with. It is comparatively easy to stimulate interest in one who has poorly developed but on the whole correct ideas concerning the subject. It is harder, of course, but not hopeless to deal with the individual who has formed erroneous ideas. It is very hard to deal with the individual who has no ideas on a subject at all.

Read the literature on cardiovascular diseases, and you find a list of indefinite and even absurd causes given for the most serious affections. You find tobacco given as the usual cause of heart disease, while, in fact, it is the cause in but few cases. You find alcohol receiving undue blame. Then again, syphilis and infectious diseases are blamed, but they can only account for a few cases. The damage to the heart from rheumatism is very definite and well known. However, the greater number of heart patients have none of these things, and have presented a profound mystery to thoughtful men in all times, while the less thoughtful writer and practitioner have accepted the inadequate causes mentioned above without question. One of the most brilliant writers on the heart of the last half century, David Wooster, of California, says:

> Permanent disease of the heart is derived from the deposition, in some portion of it, of analogous tissues; that is, analogous to healthy tissues. The cartilage and bone deposited in the heart and arteries is analogous to cartilage and bone in the joints, though not exactly like, either chemically or physiologically. It

is disease of the heart caused by these deposits and that caused by the deposition of fat in the substance of the heart and also that caused by atheromatous deposits, either alone or in company with cartilage and bone, with which we are most concerned.

We are accustomed to say that heart disease comes of itself. If one has an inflamed eye, we say that the eye has been recently hurt or exposed to a cold wind or some contagion; if one has a fever, we say he has been exposed to its cause recently. We recognize these causes, and always refer to them for the solution of the phenomena of acute affections. Not so with chronic diseases. We are apt to say they come of themselves, and yet they have causes as definite and appreciable as an intermittent fever or a pneumonia, but they are so long in acting that we keep no record of them and do not seek them until the disease takes form and place.

We do not know why this premature old age seizes on the heart rather than the lungs or liver; why it does not at the same time cause wrinkles and parchment coloration of the skin. These negative inquiries are unprofitable, and if answered would not elucidate the unsolved problem, Why are analogous growths deposited in the heart at all? They are deposited because one dissipates. But why does dissipation cause them? Because it induces old age. But why does old age cause these deposits? Because nutrition is defective, and hence the form elements are dwarfed and imperfect. But why is nutrition defective in old age? Here the oracle returns no longer any satisfactory answer, and hence the first question remains unanswered and unanswerable; that is, we do not and probably never can know why analogous growths are deposited in the heart at all.

Undue importance has been attached to disease of the coronary arteries, but, in fact, is an element in only a very small proportion of cases, and with a great majority of mankind there is never any question of great muscular strain or external violence.

Much closer to the truth, but not within its light, are the large number of authors who lay great stress on gout as a cause of hardening blood vessel disease in those past middle life. These at least recognize a chemical cause.

My own belief is that most cases of cardiovascular disease developing past middle life are instances of chronic amino-acid or other split product poisoning, and that the condition known as intestinal putrefaction has an important bearing on the matter, though it does not seem to me that it is as straightforward an instance of bacterial disease as many at the present time maintain.

If we look about us in the world, we see many examples of persons who are poisoned by particular articles of food; that is, poisoned in a way that makes them immediately and uncomfortably ill. Many other people eating the same food escape harm, and we say that the people who have been made ill are idiosyncratic to that particular kind of food.

Heart disease seems to me often to develop as a result of damage done by some material derived from food to which the tissues are idiosyncratic. The damage also often comes about gradually with-

out disagreeable symptoms. The substances at fault are in all probability the split products derived from the breaking down in the intestinal tract of nitrogenous food derived from eggs, fish, meat, and soups. Which of these foods supply the amino acids or other split products doing the damage can only be determined by experiment with the individual under observation. We can not lay down rules for everyone. Thus, I have observed examples in which almost fatal heart disease developed from the excessive eating of fish; many others are damaged by an excess of eggs; and still a greater number by meat. When the process is started, even a very small quantity of the offending food can keep the damage going on.

Of late years it has become fashionable to consider this whole matter one of intestinal putrefaction. This seems to be going too far, but it is a fact that the chemical manifestation of the condition known as intestinal putrefaction, as shown by indican in the urine, is a usual accompaniment of this poisoning. I have seen very bad cases in which it was absent.

The early signs of heart disease are the early signs of poisoning, or protein split product toxicardia, namely, disturbances of heart action, in the form of rapidity, or premature contractions, and a sense of oppression, pain over the heart, and shortness of breath on exertion, and poor circulation.

A similar poison may attack the nerves and cause neurasthenia or cause recurrent headaches. The combination of headaches and palpitation is quite common.

These symptoms have often been described as dyspepsia, without any very definite idea as to what was meant by the term. Dyspepsia in itself hardly ever affects the heart. It is the products of a wrong chemistry of the protein food that does this.

The study of many thousands of specimens and of a great number of patients leads me to the belief that the natural course of the development of heart disease is as follows: At first the patient has no symptoms. Heart disease, in its early stages, has no symptoms, no acidity of the stomach, no constipation—nothing. The first thing that is noticed, if there is an accidental examination of the urine, is the presence of indican, or the derivatives of skatol or phenol, one or all of the putrefaction group. The patient has no symptoms until one of several things happens. After a long time the patient may have an attack of hemiplegia, or quite early he may have an attack of neurasthenia; then the condition is recognized. In the latter case the patient undergoes treatment, is sent away, and frequently escapes arteriosclerosis. If he happens to escape nervous symptoms, he goes on for a good many years, possibly excreting indican (being the index of various toxines), and then after a while the excretion of these products through the kidneys damages them. Then albumi-

nuria develops and a few hyaline casts appear. These are often discovered by life-insurance examiners, which is a very fortunate thing. If this is not the case, the myocardium often becomes involved. The arteries are affected last. So, some trouble with the myocardium develops in the patient, he has a soft murmur, and slight dilatation of the heart; or else præcordial pain, which is explained by the reflex protective phenomenon, which consists of the fact that whenever an unstriped muscular tissue is unable to do its work it irritates that level of the spinal cord, and the sensory nerves passing through it are irritated, so that the nerve gives rise to pain that is felt in the brain and referred to the distribution of the nerve. The little boy who eats the green apple has the same kind of pain, and it is exactly analogous to the failure of the heart muscle which is poisoned by amino acids and has difficulty in doing its work.

Now, if the patient escapes cardiac symptoms and neurasthenia, and albuminuria is not discovered, then last of all the blood vessels are affected. The blood vessels are not affected so much directly, but indirectly, through the kidneys. The kidneys are damaged and unable to do their work, except with additional blood pressure; so when the kidneys are unable to do their work properly blood pressure is raised. It is a compensatory phenomenon. When the blood pressure is raised the heart becomes hypertrophied to more easily keep up the blood pressure and the blood vessels themselves become hypertrophied for the same reason. We have at first the hypertrophy of the blood vessels and later the deposit of fibrous tissue.

I should say that in the early stages of this condition, when the toxic elements are active, though excreted, and the structural changes have not taken place in the kidneys enough to increase blood pressure, these patients have low blood pressure because of the disturbance of the tone of the heart muscle and the muscular elements of the blood vessels. The moment the kidneys become at all incompetent there is a tendency to high blood pressure.

Thus we have a vicious circle—we have the hypertrophied heart and blood vessels and the damaged kidneys. The kidneys and blood vessels are progressively damaged, and at the end of 25 or 30 years the patient, who started with indicanuria, has changed into a typical case of Bright's disease, with hypertrophied heart and blood vessels and liability to terminal apoplexy, uræmia, or cardiac dilatation. This is the natural history of a case of heart disease.

So much for a general consideration of the subject, which is necessary to the logical conclusion with reference to prevention.

The importance of intestinal putrefaction has been dwelt upon by many writers and is no doubt a long step in the right direction. A low protein diet seemed at the time when it was advocated a great advance in accomplishing good, as is often the case, even if adminis-

tered under a misconception. I now believe in and advocate the *few protein diet*, which seems to justify itself by the results I have observed. It is founded on the belief that heart disease is not caused by a high protein diet as such, but by the action of some amino acid or other split product derived from some particular protein food or foods to which the individual attacked is idiosyncratic. I believe, as mentioned above, that conscious poisoning of many individuals by particular protein derivatives points in this direction.

So a person eating the great variety of protein foods found in a modern dietary is laying himself open to the attack of many different kinds of split products, any one of which may be the one which is to do him harm. If he cuts out one-half of his proteins he is by that much safer. If he is willing to do with a single protein he is almost certain, on the theory of chances, to escape that which will do him damage.

In Dr. Chittenden's laboratory it has been shown that animals get along fairly well through several generations on single proteins. I have also abundantly proved that human beings sick with heart disease not only can stand a single protein diet, but usually become improved when on it.

This theory explains to me several things that have always been obscure, namely, in the first place, the relative unfruitfulness of the quantitative investigation of the nitrogen intake and outgo in disease. The matter being one of quality and not of quantity, the reason becomes plain enough.

The fact that the poisoning is not the same in every case nor, indeed, often in any two cases, explains the great variety of different combinations of symptoms. In one patient migraine is very prominent; in another, pain derived from the heart muscle; in another the kidneys are early affected; in others the nervous system is profoundly involved.

The prevention of heart disease in otherwise healthy individuals past middle life is a matter of dietetic management and the avoidance of all those things which may upset the chemistry of the body. The chemistry of the body can be upset by nerve strain, anxiety, and stress; it can be upset by the abuse of drugs, particularly the saline laxatives and mineral waters; it can be profoundly upset by accidental food poisoning. It can be disordered by an acute illness, particularly one involving the liver. Nor should we forget the necessity of rest and exercise.

In the presence of any suspicion of commencing trouble a course of treatment should be taken consisting of castor oil and a temporary diet from which eggs, fish, meat, and soups are excluded, cheese being allowed to supply nitrogen in the safest form. When the danger seems to be past the protein food should be added one article

at a time, as, for instance, meat once a day, and later eggs or fish; but the number of kinds of protein food must be kept within limits according to the condition of the individual. At first the person may be idiosyncratic to only one or two forms of food. A person with advanced heart disease is idiosyncratic to most forms of protein food. A very thoughtful physician, Dr. Edward Cornwall, of Brooklyn, said in a recent article:

> In this connection I should like to call attention to the value of dietetic treatment in the prophylaxis of cardiovascular disease. Many individuals are destined from their birth to die of this disease. Even if they take ordinarily good care of themselves when middle life comes their their heart, arteries, or kidneys begin to wear out. This may be due to the poor material of which their vascular system is made or to abnormally functioning organs, especially an insufficient liver. Whatever may be the particular weakness in their makeup, that weakness should be favored. This can best be done when we suspect an individual of being in this predestined class—and the suspicion is always excited by a family history of apoplexy, Bright's disease, diabetes, obesity, or chronic rheumatism—by giving him an antiputrefactive diet, which is approximately, though not necessarily, completely lacto-vegetarian and which is limited in quantity to his physiological requirements, and by starting him on that diet as early as possible. And those who engage in the strenuous life, especially in the cities, living this strenuous life differently from their ancestors and unhygienically, can with advantage make the work which their food puts on their already strained cardiovascular system as light as possible by such dietetic prophylaxis.

Much of this is true. In concluding these remarks, I would like to emphasize the following points:

The causes and prevention of heart disease have been considered in the past, as shown by my quotation, as matters of great obscurity, and often placed on the shoulders of Providence.

I would like to emphasize the analogy between the universally recognized idiosyncracy of some individuals to particular articles of protein food that produce in them symptoms of pain, and the unconscious idiosyncracy of many others to split products derived from protein which produce damage without conscious symptoms.

I would like to urge the importance of periodic chemical examinations of supposedly healthy individuals past middle life to detect and correct conditions that would lead to heart disease.

I would like to again express my belief that the abuse of saline laxatives and their disturbing influence on the chemistry of the body tend to the production of heart disease, leaving castor oil now, as ever, the safest and best remedy for those threatened with protein poisoning.

Lastly, those attacked with a tendency to heart disease must receive courses of treatment at intervals, such as are so finely developed in the cure resorts of Europe, and which we are now adopting in America, and which can be found in New York and other great cities.

THE PHYSIOLOGICAL HYGIENE OF WORK IN COMPRESSED AIR.[1]

J. J. R. Macleod, Physiological Department, Western Reserve University, Cleveland, Ohio.

It is now a well-established fact that the symptoms from which caisson workers and deep-sea divers are so often liable to suffer, during or shortly after they return from the increased air pressure to the atmospheric, are due to the development of bubbles of nitrogen in the body fluids and tissues. While subjected to the increased pressure the latter dissolve air in direct proportion to the pressure, the blood, first of all, and, later, the more remote parts. So far, the physical condition of the blood does not become altered; it circulates as freely as before, and the tissues remain perfectly normal in structure. If the pressure be now very gradually lowered, the excess of dissolved gas will be so slowly thrown out of solution that it will be discharged into the alveolar air without any of it appearing in a free state as bubbles in the blood; but, if the decompression be more rapid, the gas will be discharged too quickly to permit of its removal before free gas has formed, so that the blood and tissues will become loaded with bubbles.

The appreciation of these principles has led in recent years to the adoption of methods of safeguarding the workers against the development of symptoms, and of treating them when these appear, that have rendered work in compressed air incomparably safer than formerly. There are, however, several details in connection with the practical application of these principles that remain to be evolved, and it is more especially with regard to these details that we will deal in the present paper. They may be classified under (1) the working conditions while under the compresed air, and (2) the safeguards against the development of symptoms during or after decompression.

The working conditions in a caisson are somewhat different from those at atmospheric pressure, on account of the fact that the air, by its compression, is warmer and is loaded to saturation point with moisture. It has also been thought that the supposed harmful influence of carbon dioxide would become exaggerated in compressed air, and, indeed, one investigator, Snell, has attributed the cause of the illness to this gas. It can easily be shown, however, that such is not the case, but that, as in ventilation at atmospheric pressure, the percentage of carbon dioxide serves merely as a convenient indicator of the adequacy of any system of ventilation. The baneful influence of the hot, wet air in the caisson depends on its interference with the heat-regulating mechanism of the body. By doing muscular work the temperature of the body tends to rise; under ordinary conditions

this rise is prevented by increased dissipation of heat from the surface of the body, brought about partly by increased radiation and partly by the evaporation of sweat.

In warm, moist air, however, neither of these mechanisms can operate, and as a consequence the body temperature does not become properly adjusted, the workman feels uncomfortable and disinclined for hard work, the skin becomes flushed and warm, and there is excessive perspiration. When such working conditions are repeated day by day the appetite is likely to fail, partly because of the tendency of the body to suppress the activity of the metabolic processes, so as to keep down heat production, and partly, no doubt, because the digestive processes are working below par on account of there being less blood circulating through the visceral blood vessels; it has been sent to the surface of the body to be cooled off. The worker therefore tends to take less food, his metabolism becomes depressed, and his factors of safety against bacterial infections become lessened.

The risk of symptoms appearing on decompression is also greater when the air in the caisson has been moist and hot, for the heart has been overworking to maintain the blood flow in the dilated vessels; it gets fatigued and is consequently unable to maintain, during decompression, a rate of blood flow that is adequate for carrying the gas-saturated blood to the lungs where the excess of gas becomes dissipated.

The criterion of proper working conditions in the caisson is therefore the wet-bulb temperature. This should stand below 75° F. To maintain such conditions it is necessary to ventilate the caisson, preferably with air that has been cooled by cold-water radiators; in any case, the ventilation should be adequate to keep down the wet-bulb temperature. The increased expense of ventilation with cooled air would soon be balanced by the greater working efficiency of the men. Constant circulation of the air in the caissons by means of fans assists also in improving the conditions, for it will help to increase dissipation of heat from the body.

As illustrating the relative importance of the physical condition of the air, as against the percentage of carbon dioxide, as a factor in producing the baneful effect of a confined atmosphere, the following experiment, recorded by Leonard Hill, is most instructive:

Eight students were shut up in an air-tight chamber, and after 44 minutes the wet bulb reading was 83° F. and the percentage of CO_2 5.26 per cent. During all of this time the students were becoming progressively affected; full of fun and hilarity at the start, they became before long quiet and uncomfortable. The air was then made to circulate by turning on electric fans, and although the CO_2 and the temperature continued to rise the students immediately felt

which, however, immediately returned when the fans were shut off.

Equally striking results have been obtained by observing the pulse rate following muscular work in relation to humidity and chemical purity of the air. With the wet bulb between 86° F. and 97° F., in an atmosphere containing no CO_2, the pulse rate for the first minute after work was 142, falling in the next minute to 118. With the wet bulb practically the same in an atmosphere containing about 5 per cent CO_2 and 16.7 per cent O_2, the minute pulse rates following the same amount of work were 148, 144, and 136. With the wet bulb lowered by 20° F. by means of artificial cooling and fans, but the CO_2 and O_2 the same, the rates were 134, 110, and 104.

Turning now to the control of decompression, a great many interesting and important considerations have recently been submitted, especially by Haldane, Boycott, and Damant, who undertook an investigation of the question for the British Admiralty, and by Hill and his collaborators. The most important of these concern the relative value of gradual and stage decompression. To understand the principles governing the desaturation of the body, we must go a little more fully into the question of the distribution of the dissolved gas in the body, while the pressure is rising and falling. For this purpose we may consider that the only gas concerned is nitrogen. The blood in the capillaries of the lungs must dissolve nitrogen in proportion to the pressure of this gas in the alveoli; the blood carries the dissolved gas to the tissues and these dissolve it until the pressure is again equalized between them and the blood. The blood, after giving up its excess of dissolved nitrogen, returns to the lungs and again becomes saturated, and this goes on until blood and tissue have become saturated with gas at the external pressure. The tissues are two-thirds water and they contain (in man) from 15 to 20 per cent of fat. Fat, however, dissolves five times more nitrogen than water (Vernon), consequently, it takes longer for a given volume of tissue than of blood to become saturated at a given pressure.

The blood in man constitutes one-twentieth of the body weight; so that if the tissues were all liquid they would dissolve 20 times as much nitrogen as the blood. On account of the fat which they contain, however, the tissues take up more than this proportion, namely, in an average man about 35 times more than the blood. All the blood in the body takes about one minute to complete a round of the circulation, so that in this time, after being suddenly subjected to an increased pressure, assuming that the blood circulates equally throughout the body, the tissues will be one-thirty-fifth saturated; in the next minute another thirty-fifth of thirty-four thirty-fifths will be saturated, and so on. After five minutes the body will be

about 22 per cent and in 25 minutes about one-half saturated; but it will take about two hours before saturation is complete. These calculations assume that the blood is evenly distributed throughout the body, but this is not the case, for its mass movement varies considerably in different parts, being much greater in the active muscles and in the glands than in passive structures, such as fat and in the joints. These less vascular parts will therefore lag behind the others in taking up their full quota of gas, and therefore prolong the time necessary for complete saturation of the body as a whole.

We see therefore that, after some time in compressed air, the blood and active tissues will be saturated and contain volumes of dissolved gas in proportion to their relative bulks; the fat, although not saturated, will yet contain up to five times more gas than an equal volume of blood and the passive tissues will be incompletely saturated.

These considerations regarding the saturation of the different parts of the body apply also in its desaturation. Suppose, for example, that the external pressure is suddenly lowered; the blood, on leaving the lungs, will contain no excess of gas; when it reaches the tissues it will remove gas until the pressure is equalized, discharge this into the alveoli and return again for more. Other things being equal, it will take the same number of minutes to desaturate that it took to saturate, and the parts of the body that will lag behind the others, in being dissaturated, are those with a sluggish circulation.

When the mass movement of the blood is increased by muscular exercise, the rate of saturation and desaturation with nitrogen is increased in proportion. During active work the increase in movement of the blood may be four or five times over the normal, so that the tissues of the caisson worker become much more quickly desaturated than the above figures would lead one to expect.

With regard to the application of these principles in the practice of decompression, it is evidently impracticable to occupy so much time in doing this as it has taken to saturate the body. We must therefore determine what difference of pressure between the external air and the body may be allowed without any of the dissolved gas forming bubbles. Haldane points out that experience shows that there is no risk of bubbles forming unless the air pressure exceeds 20 pounds, or, allowing 5 pounds as a margin of safety, it is impossible for any bubble formation to occur, however quickly the decompression, after exposure to + 15 pounds pressure (i. e., 2 atmospheres absolute). "Now, the volume of gas capable of being liberated on decompression to any given pressure is the same, if the relative diminution of pressure is the same." (Haldane.) On reduction from 4 to 2 atmospheres, the same volume of gas will tend to be liberated as on reduction from 2 to 1 atmospheres, that is to say, no

bubbles will form. The practical conclusion is "that the absolute air pressure can always be reduced to half the absolute pressure at which the tissues are saturated without risk." Thus, after saturation at 90 pounds absolute pressure (+ 5 atmospheres), a man can be immediately decompressed to 45 pounds (+ 2 atmospheres) in a few minutes without risk, but from this point on the decompression must be conducted slowly, so as to insure that the nitrogen pressure in the tissues is never more than twice the air pressure. The great advantage of this method is that it makes the greatest possible use of difference of pressure between tissues and blood in order to get rid of the gas that those contain.

When the decompression from the start is gradual the desaturation of the tissues will progressively lag behind that of the blood, and the tendency to the liberation of free gas will become greater. To make this clear, let us suppose that the body is saturated at 40 pounds pressure, and that the pressure is lowered by 2 pounds per minute. At the end of five minutes, the pressure will be 30 pounds, or an average of 35 pounds during the five minutes. In this time, about 20 per cent of the excess of nitrogen would disappear, that is to say, 20 per cent of the difference between 40 pounds and 35 pounds, so that the pressure of nitrogen in the tissues will now correspond to saturation at 39 pounds pressure or 9 pounds above the actual air pressure. At the end of the next five-minute period, the pressure in the air will be 20 pounds, but in the tissues it will be 36.2 pounds $\left(39-\frac{39-25}{5}\right)$, or 16.2 pounds higher; and, by applying the same calculation, this difference, by the time atmosphere pressure is reached, will amount to 26.5 pounds, which, as we have seen, will very likely cause bubbles to appear.

When the decompression is continuous from the start, it is far too slow at first and far too rapid later. Theoretically, therefore, the decompression should be rapid at first and very slow later.

Time will not permit of our considering the numerous experiments of Haldane, and of Hill, and their respective associates, in testing these considerations. It is enough to say that, although it has been shown by both schools that stage decompression is somewhat safer than gradual decompression, the difference is not so great as might be expected on theoretical grounds. On decompressing goats that had been for varying periods of time in + 75 pounds pressure, partly by the stage and partly by the uniform method, Boycott and Damant found the former to be decidedly safer, for 82 per cent showed no symptoms, whereas, by the uniform method, only 47 per cent went free. The advantage of the stage decompression is particularly after short exposures. On the other hand, Hill and Greenwood, using pigs and rabbits, could make out no definite advantage for the stage

method. The two methods have also been compared in actual caisson work at the Elbe Tunnel, where the pressure was + 2 atmospheres. Very little advantage could be demonstrated for the stage as compared with the uniform method at this comparatively low pressure. The general conclusion, which we may draw, is that the stage method should be employed, although it is not to be expected that it will absolutely insure absence of decompression symptoms.

Regarding the permissible initial drop in pressure, and the duration of the succeeding decompression, working tables, based on the above experimental work, have been issued by the admiralty committee, and, more recently, by Japp, who found, in actual practice, that the older tables were impracticable on account of the length of time required. Japp bases his table on the assumption that there is little risk of bubble formation when decompression from 27 pounds is effected in 9 minutes, and he has shown, in his extensive practice at the East River tunnels, that his working table is safe and that it is possible to persuade the workmen to adopt it.

There are two other factors that are to be considered in hastening the desaturation of the tissues; these are muscular exercise, and the breathing of an indifferent gas.

It is clear, from what has already been said, that the gas dissolved in the tissues will become removed in proportion to the mass movement of the blood, and it is probably true that muscular exercise, performed in the decompression chamber, is of as great importance in preventing the subsequent development of symptoms as a much prolonged decompression. In a man at rest, the circulation through the central nervous system and the viscera is constantly influenced by the pumping action of the respiratory movements, but in the capillaries of the muscle joints, fat, etc., this influence is not felt and the blood flows more slowly. It is consequently in these parts that bubble formation is likely to occur, especially some time after decompression. The bubbles cause the neuralgic pains; the "bends" and "screws" so well known to caisson workers. These could no doubt be entirely prevented by muscular exercise and massage of the limbs during decomposition. In illustration of these facts the following experiment by Greenwood may be cited: During decompression from +75 pounds pressure in 95 minutes "Greenwood flexed and extended all the limb joints at frequent intervals, with the exception of the knees. Subsequently pain and stiffness were experienced in the knees and nowhere else." In another experiment the knees also were flexed and no pain was felt.

But even in the parts with active circulation, the gas in the tissues may lag considerably behind that in the blood, even when the decompression has been properly controlled. This has been very cleverly

shown by Leonard Hill in the case of the kidney. The "tissue" gas in this case can be taken as the gas dissolved in the urine, by analyzing which, therefore, at different stages of decompression, the excess of nitrogen, over which it should be at the external pressure, can be ascertained. Hill and his coworkers have found, on decompression from +30 pounds by two stages to zero, that a considerable supersaturation existed. To expel this excess of nitrogen the effect of breathing oxygen was tried, and it was very definitely shown that the dissolved nitrogen could be lowered to one-quarter the normal amount. "The results show that the excess of nitrogen can be cleared out of the kidneys rapidly and completely by breathing oxygen, and this would make it safe to shorten the stages of decompression considerably." (L. Hill.)

When symptoms do appear, they can, in most cases, be relieved by recompression, and all modern caisson works are provided with a special chamber for this purpose. We need scarcely say anything about this treatment here, as its value is so well known. Suffice it to say that although it is most likely to afford relief when applied as soon as possible after the appearance of the symptoms, yet it is often efficacious when applied several days after their onset.

[1]Although the writer was previously associated with Leonard Hill in some of the work embodied in this paper, he has not been recently so engaged. The paper is, therefore, in large part a compilation from the recent literature, especially from Hill's Caisson Sickness, London, 1912, in which full references to the work of Haldane, von Schrötter, Keays, and others will be found.

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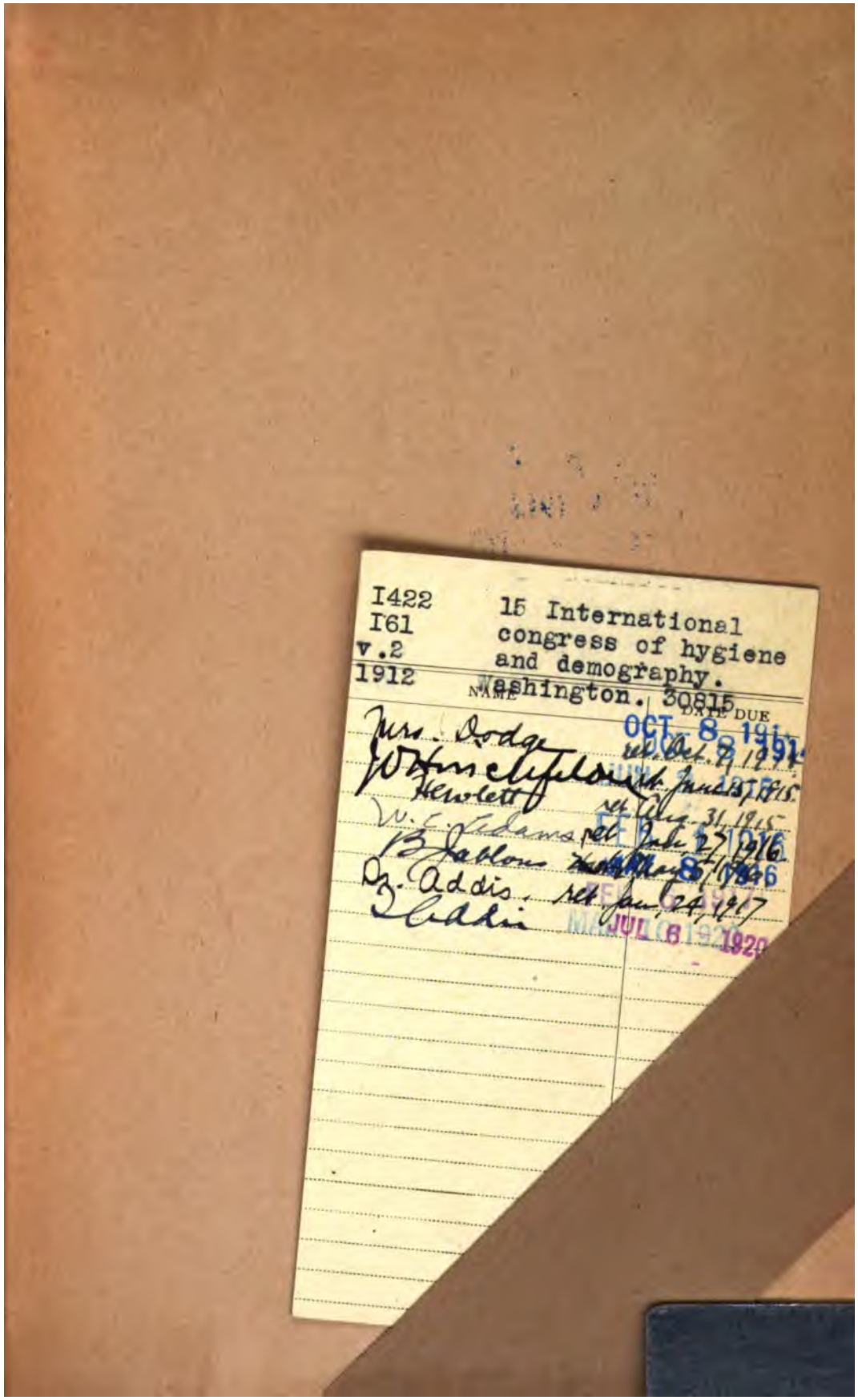
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Mrs. Dodge
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Dr. Addis.
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